STUDIES IN THE AZULENE AND TROPOLONE SERIES.

A Thesis for the degree of Ph.D.

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Contents.

Part I - Azulenes.

Summary.

A new synthesis of azulene is described. Suberone is condensed with diethyl succinate, the product (XXIII) cyclised and the resulting keto-ester hydrolysed and decarboxylated to 1-keto-octahydroazulene (XXIV). This has been reduced by aluminium isopropoxide to the corresponding carbinol, and by the Clemmensen method, after hydrogenation of the double bond, to decahydroazulene. These products have been dehydrogenated to give azulene in small yields.

The synthesis of 1-phenylazulene from the ketone XXIV was attempted, but has not been successful.

A similar condensation of 2:3-benzosuberone with diethyl succinate followed by cyclisation etc. led to 1-ketohexahydrobenzazulene (XXXII) which has been reduced by various means, but dehydrogenation of the reduction products to 4:5-benzazulene has not been accomplished.

2-Methyl-6-carbethoxyazulene has been prepared by treatment of 2-methyl indane with diazoacetic ester and dehydrogenation of the product. This has been hydrolysed to the free acid, ammonolysed to the amide, and reduced with lithium aluminium hydride to 2-methyl-6-hydroxymethyl-azulene. Attempts at Hofmann degradation or lithium aluminium hydride reduction of the amide, in order to obtain amines, were unsuccessful.

Early work.

The name azulene was first given to the blue colouring matter of camomile oil[47], which has been used as a soothing agent for burns and skin irritations for a very long time. About 50 other essential oils either possess such colours or can give rise to them by treatment with acids or by dehydrogenation.

Investigation of these colouring matters made little progress until Sherndal's discovery in 1915[1] that they could be extracted from the essential oils with strong mineral acids, such as 80% phosphoric acid. A red complex is formed which dissociates on dilution with water, and the colouring matter can then be extracted with hydrocarbon solvents. In this way Sherndal obtained homogeneous materials, forming black picrates. Their formula was $C_{15}H_{18}$, indicating relationship to the sesquiterpenes.

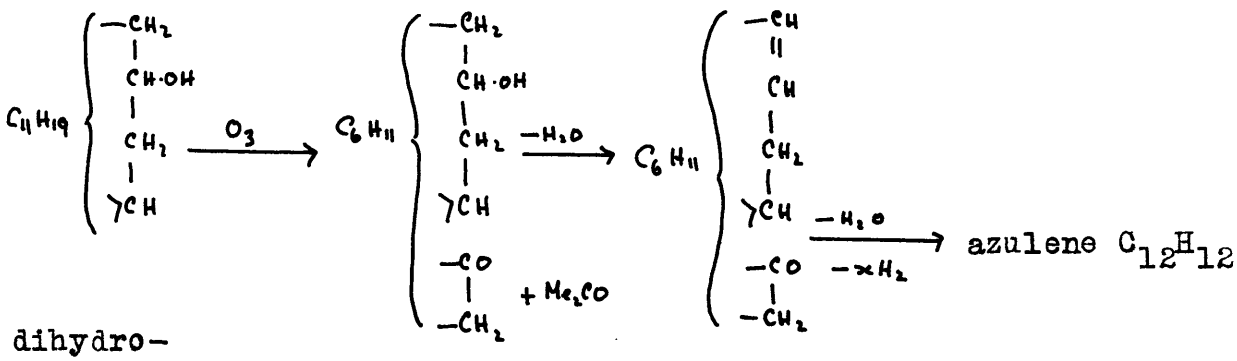
By 1936 a large number of azulenes had been isolated in this way from different sources, but on systematic comparison the number of distinct individuals was found to be only five - cham - from camomile oil, S -guaj- from sulphur dehydrogenation of guajol, Se-guaj- from selenium dehydrogenation of guajol, lactar- from the fungus lactarius deliciosus L. and vetivazulene from vetiver oil[4],[6]. These are known as the "natural" azulenes, though in fact

they are probably not present in the plant as such, but are formed during the extraction of the essential oil. They are all isomeric, having the formula $C_{15}H_{18}$, and early work showed that they contained two rings and five double bonds. Oxidation gave fragments too small to be of any use and investigation was therefore directed towards their hydrogenation products and towards the parent sesquiterpenes.

Structure.

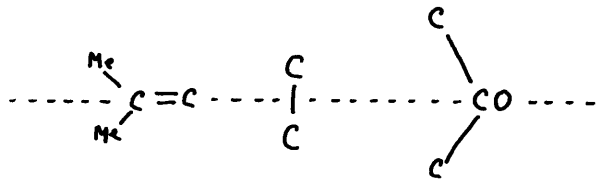
In 1936 Pfau and Plattner[6] elucidated the structure of the azulenes through a study of the related sesquiterpene ketones extracted with Girard's reagent from vetiver oil[9,10]. These ketones were converted to a mixture of semicarbazones which could be separated by crystallisation into a d- and an l-fraction, and the pure ketones regenerated from these were designated α- and β-vetivone respectively. These ketones have the formula $C_{15}H_{22}O$ and molecular refraction measurement showed that they are bicyclic and one of their two double bonds is conjugated with the keto group. Reduction of the keto group to the carbinol, followed by dehydration and dehydrogenation with Se or S led to a mixture of hydrocarbons: an azulene vetivazulene, $C_{15}H_{18}$, eudalene and 1:5-dimethyl-7-isopropyl naphthalene, the formation of the latter two compounds showing that the rings are fused ortho.

The -CH = CH - CO - system of β-vetivone was now reduced to $-CH_2 - CH_2 - CHOH-$, and the resulting dihydro-β-vetivol when subjected to ozonisation split off a molecule of acetone, indicating the presence of an isopropylidene group, to give a hydroxy ketone I, which could be dehydrated to the unsaturated ketone II. This in turn was further reduced, dehydrated and dehydrogenated to an azulene $C_{12}H_{12}$.

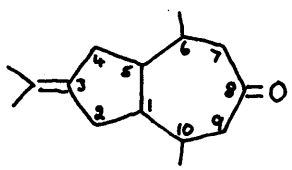


dihydro-β-vetivol I II

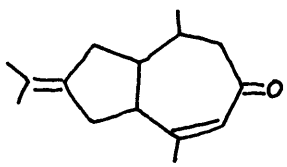
If the reduction of β-vetivone to dihydro-β-vetivol was carried out with sodium in alcohol, then the subsequent degradation products, including the unsaturated ketone II, were found to be optically active; whereas if the reduction were carried out catalytically to give a stereochemically pure dihydro-β-vetivol, then the subsequent products were found to be inactive, yet gave no m.p. depression with the other series. These inactive compounds were assumed to be internally compensated, from which it follows that the system



must be present in dihydro-β-vetivone, the two rings being unequal in size, thus giving the molecule an axis of symmetry. Since dihydro-β-vetivone forms a dibenzylidene derivative it can therefore be formulated in accordance with the isoprene rule as III, the corresponding structure for β-vetivone being IV.

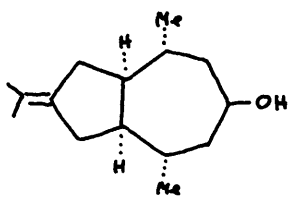


III

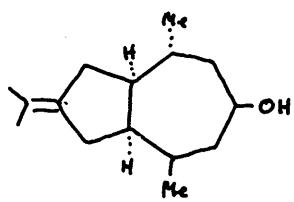


IV

These formulae explain the facts if it is assumed (a) that the rings are fused in a cis position, and (b) that catalytic hydrogenation of IV directs the Me on C_{10} cis to the Me on C_6, resulting in an inactive compound (V), while Na/EtOH produces the opposite result (VI), at any rate in part.

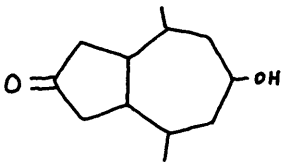


V

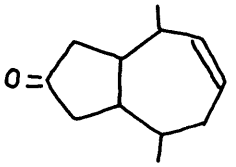


VI

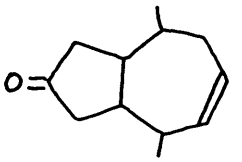
Thus the derivatives of V are inactive, and those of VI active. Dehydration of the hydroxy ketone VII can take place in two directions, giving equal amounts of VIII and IX,



VII



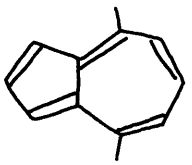
VIII



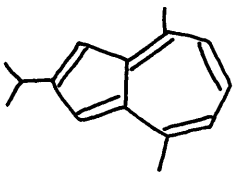
IX

which, if the meso form is used, are optical antipodes so that the product is a racemate of two active forms, whereas when the asymmetric form of VII is dehydrated, the products are both active, but not enantiomorphous.

On this basis, then, the azulene $C_{12}H_{12}$ would be X, and vetivazulene XI, these being the normal dehydrogenation products, the naphthalenes being produced by rearrangement.

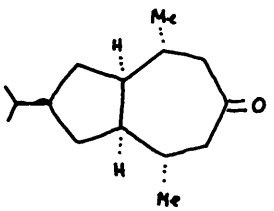


X

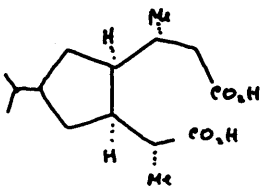


XI

This cyclopentano-cycloheptane skeleton was now confirmed by oxidative degradation. The tetrahydro-β-vetivone XII was oxidised to the dicarboxylic acid XIII, which could then be ring closed to the apo-ketone XIV followed by dehydrogenation to the known indanol XV,



XII



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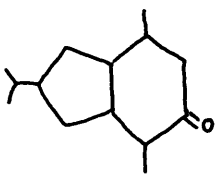
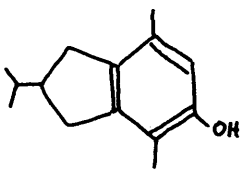
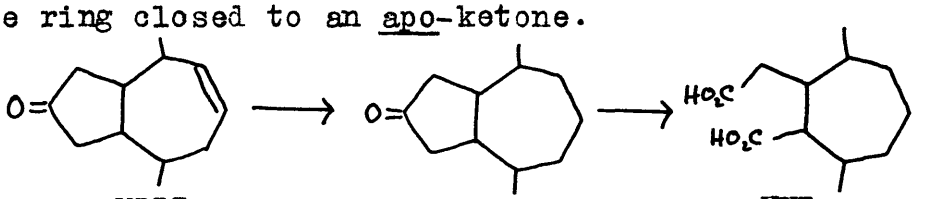


XIV



XV

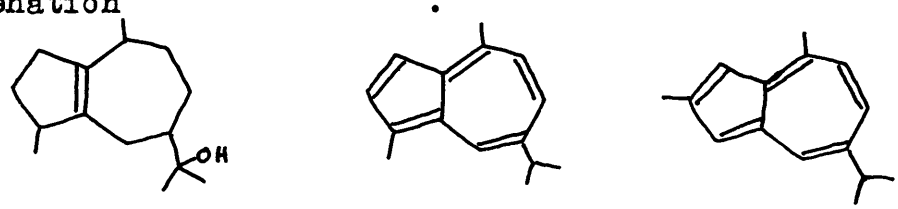
thus confirming the presence of a 7-membered ring in the original. The presence of a 5-membered ring was similarly shown by oxidation of the ketone VIII, after hydrogenation of the double bond, to a dicarboxylic acid XVI which could not be ring closed to an apo-ketone.



VIII XVI

Final confirmation was obtained by synthesis of vetivazulene[8].

A similar investigation of the sesquiterpene alcohol guajol led to the establishment of the structure XVII, and the *S*-guajazulene formed from it by S dehydrogenation was shown to be XVIII, while Se-guajazulene is considered to be XIX, formed by migration of the 1-Me group to the 2-position under the influence of the higher temperature of the Se dehydrogenation[11,12,13,14,15].

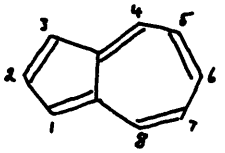


XVII XVIII XIX

In addition to lactarazulene, the fungus lactarius deliciosis L. contains an interesting violet pigment, lactaroviolin, which has been shown to be an isopropenyl

azulene-aldehyde[33,34,59,60].

The parent structure of the azulenes then, is the bicyclo (0:3:5)-decapentaene skeleton. This compound is now called "azulene" and is numbered thus:



Vetivazulene is therefore 4:8-dimethyl-2-isopropyl-azulene, and S-guajazulene is 1:4-dimethyl-7-isopropylazulene.

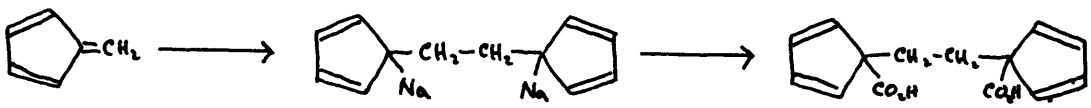
Properties.

Very little is known of the chemical properties of the azulenes. The polysubstituted azulenes obtained from natural sources are liquids or low-melting solids and are quite stable. The parent hydrocarbon $C_{10}H_8$ is not so stable however and resinifies slowly on standing. It is a solid m.p. 99°, the highest m.p. of any known azulene hydrocarbon with the exception only of 2-phenylazulene which melts at 230°. Addition complexes with picric acid, styphnic acid and trinitro-benzene are also formed and these can be broken down by chromatography on alumina, with petroleum as solvent, the hydrocarbon being more easily eluted. Azulene itself in fact is not adsorbed at all by alumina and passes straight through the column[7]. No isomers have been found to indicate fixation of the double

bonds, and a resonance energy of 46 k. cal per molecule has been calculated for azulene as against 74 k.cal/mol. for naphthalene[36].

These properties seem to indicate that azulene is a mesomeric system with at least some degree of aromatic character.

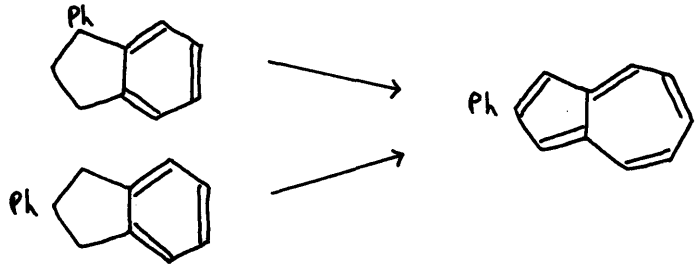
The formation of a sodium derivative in the absence of air, giving an acid with CO_2, is described[5c,d]. Similar compounds are known to be formed in the fulvene series.



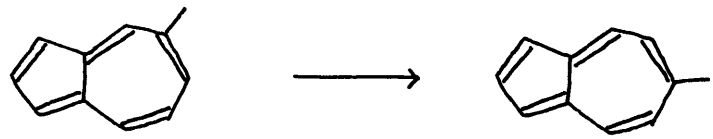
The formation of a sulphonic acid by treating a natural azulene with Ac_2O and H_2SO_4 is reported, and alkali salts of this have been isolated[1]. Bromination is said to result in the addition of 4 atoms of bromine and the substitution of one[5b]; but these properties are based on single, isolated observations and require further investigation. The blue colour disappears after the uptake of ~ 2.5 molecules of H_2[5c].

Azulene itself can be transformed into naphthalene by heating to about 300° in a sealed tube[35,36], and substituents in certain positions on the azulene nucleus appear to be specially prone to migration at high temperatures. For example, the migration of a methyl group from the 1- to

the 2-position during Se dehydrogenation of guajol[26] has already been mentioned, and it has been established that 2-phenyl-azulene only is formed, irrespective of whether 1-phenyl- or 2-phenyl-indane is used as starting material[30].



Similarly 5-methylazulene is found to change into 6-methyl-azulene at high temperatures[23].



One of the most interesting properties of the azulenes is their solubility in strong mineral acids, first observed by Sherndal in 1915 (loc.cit.) and since very widely used for their isolation from natural sources or reaction mixtures. The acids generally used are 50-60% aq. H_2SO_4 or 85% H_3PO_4. With these the azulenes can be completely extracted from organic solvents immiscible with the acids, and by diluting the acid phase to 20-30% the azulene is quantitatively precipitated and can be re-extracted with organic solvents. If the acid solution is allowed to stand

for long in air there is sometimes a slight loss of material due to oxidation or other reactions, but this can be reduced to a minimum by using the most dilute acid possible for the extraction and working in an atmosphere of nitrogen. The parent hydrocarbon $C_{10}H_8$ is particularly unstable in acid solution.

The blue colour of the azulenes changes to orange or red in acid solution, suggesting that a reaction takes place, and this is borne out by some recent work on the distribution coefficients of various azulenes between toluene or petroleum on the one hand and H_2SO_4 or H_3PO_4 of varying concentrations on the other[56]. These coefficients K' have been shown to bear a linear relationship to the strength of acid used defined as the Hammett function H_0[57]; and the value of H_0 for which K' = 1, which is a measure of the tendency of the azulene to dissolve in the acid, is found to be characteristic for any given azulene and may therefore be used for its identification. This new physical constant is particularly valuable since it varies with the size of the alkyl substituents as well as with their positions in the nucleus, thus differentiating between, e.g., 2-ethyl-, 2-n-propyl- and 2-iso-propyl-azulenes, which is not possible by spectrographic means. This differentiation may also be used for the analysis of mixtures of known azulenes by the

fractional distribution technique of Craig[58].

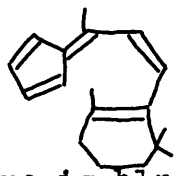
Biological properties.

The biological properties of the azulenes have been of interest since the beginning of the investigations as the soothing action of camomile oil has been known for centuries. That this soothing action is entirely due to the chamazulene content has been proved by tests against irradiation erythema on human skin and mustard oil irritation in rabbits' eyes[41,42,43]. The residual oil after the removal of the azulene has no action, nor have vetivazulene or azulene itself[44]. S- and Se-guajazulenes have been found ineffective against xerophthalmia in rats[4]. The synthesis of chamazulene would therefore be of some importance, but as yet its constitution is unknown though some inferences may be drawn from its spectrum, to which reference will be made later.

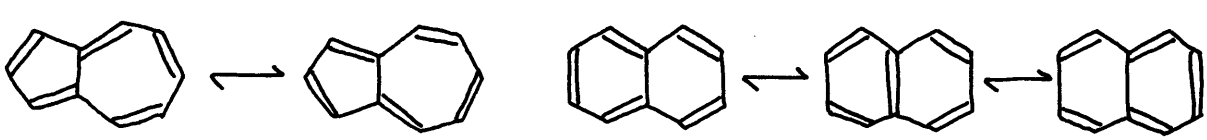
Spectra.

The most striking property of the azulenes is, of course, their intense colour, ranging from red-violet to pure blue and blue-green, especially in view of the comparatively simple structure of the compounds. The longest visible absorption band is at about 7000 Å, and to attain this in the diphenyl-polyene series, for example, a

conjugation of about 20 double bonds is required. In the more nearly related fulvene series, a conjugation of five double bonds, as in the following compound,



only produces an orange red colour and in the purely aromatic series, although pentacene is blue in the crystalline state, its longest visible absorption band is only about 5800 Å. Hence it is seen that the usual theories of colour, based on chromophores and auxochromes, do not apply in this case. By regarding the azulene molecule as a mesomeric system and applying the quantum mechanical methods of Slater and Pauling, A.L. Sklar[53] has been able to calculate the position of the longest absorption band without using spectroscopic data, and his results are in very good agreement with the observed value. In an extension of Sklar's work, Förster[54] has pointed out that the difference between azulene and naphthalene can be explained quite simply: thus for azulene only two Kekulé structures are possible, which can be interchanged by the simultaneous shift of five double bonds; while in naphthalene three such structures exist and can be interchanged stepwise by a shift of only three double bonds at a time. Hence



naphthalene must resemble benzene in its absorption spectrum, while azulene should resemble the as yet unknown cyclodecapentaene, the bridge bond having no importance in the resonance.

The entry of alkyl substituents into the azulene nucleus produces a regular shift in the spectrum which can be of use in identifying unknown compounds. The spectra of the substituted azulenes can be divided into two definite groups depending on whether the 2-position is substituted or not[26]. If the 2-position is unsubstituted a fairly simple type of spectrum is obtained, the bands being spaced regularly and the sequence of intensities being the same in all cases. The entry of a substituent in the 7-membered ring produces a shift of about 15 mμ in the wave lengths of the bands, the direction of the shift alternating with the position of the substituent. Thus a substituent in the 4- or 8-position shifts the absorption towards the blue and the colour towards the red, while substitution in the 5- or 7-position has the opposite effect[28,24]. Substitution in the 6-position again shifts the colour to the red[19]. This shift depends only on the position and not on the size of the group, and it is additive, so that the shift for a poly-substituted azulene can be calculated by adding the

shifts produced by each substituent singly. Substitution in the 1- or 3-position produces a larger shift, of about 40 mμ towards the red, the colour changing to the blue; but substitution in the 2-position alters the character of the spectrum completely, producing a more complex series of bands. The alternating effect still holds, however, since the colour is changed towards the red. Although the bands in the simple 2-alkylated azulenes are sharp and well-defined, further substitution produces diffuse spectra such as those of Se-guaj- or vetivazulenes in which the bands are weak and their centres difficult to determine. Despite this, the same relationships appear to hold as in the first group.

These spectroscopic data have been of use in settling doubts as to the constitution of synthetic azulenes, for example where the diazo-acetic ester method of synthesis gives anomalous results (see later). Thus the difference between 5-methyl- and 6-methylazulene is readily settled, the former being more blue and the latter more red than azulene itself[24,28]. The natural blue azulenes cham-, lactar- and guajazulenes have almost identical spectra, and guajazulene is known to be 1:4-dimethyl-7-isopropylazulene; from which it can be inferred that the other two are substituted in the same, or equivalent positions (e.g., 1:5:8; 1:5:6; or 1:7:8-)[25].

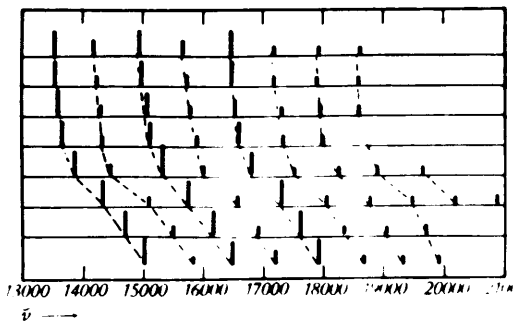


Fig. I.

Absorptionsbanden der Azulene der ersten Gruppe.

Die Wellenzahlen ($\tilde{\nu}$) der Banden sind den Tabellen entnommen. Die Höhe der Banden entspricht den beobachteten Intensitäten. Die sich entsprechenden sind durch punktierte Linien miteinander verbunden.

Absorption bands of azulenes in the first spectrum group.

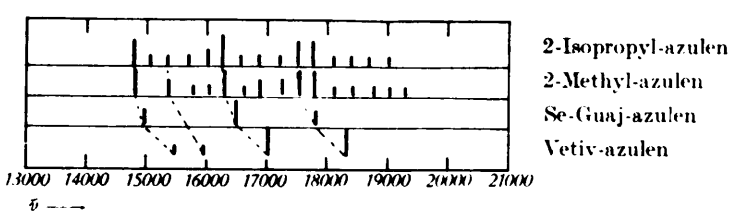


Fig. II.

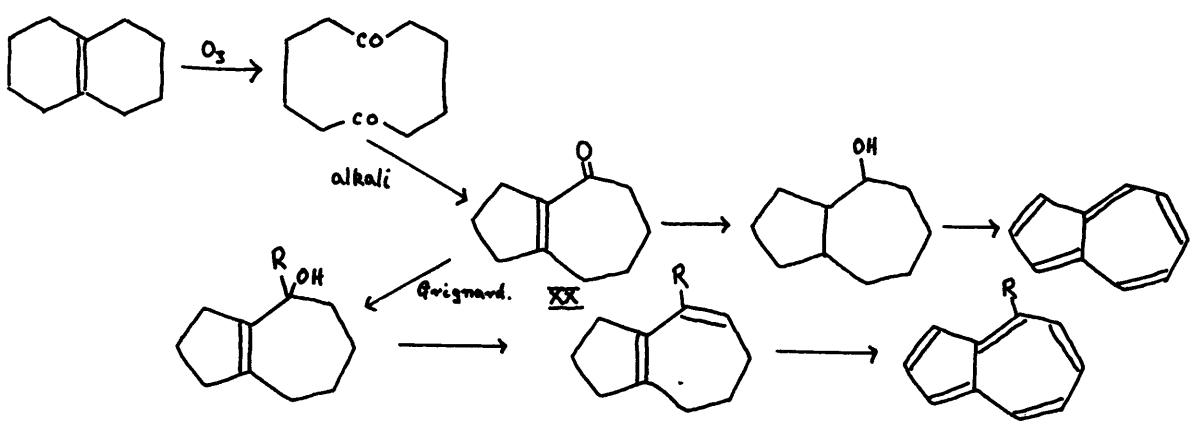
Absorptionsbanden der Azulene der zweiten Gruppe.

Absorption bands of azulenes in the second spectrum group.

Some studies in X-ray[55,83] and infra-red[84] spectra have also been made.

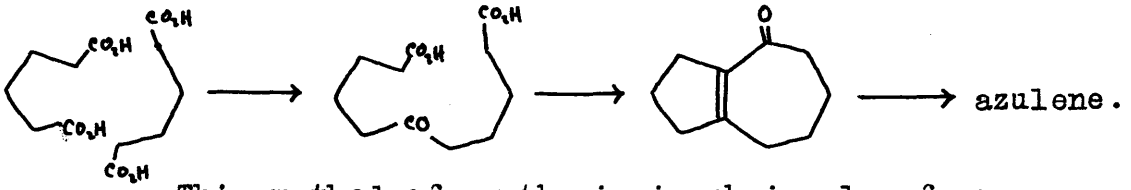
Synthesis.

Previous to 1936 the only compound known to contain the cyclo-pentano-cycloheptane ring system was the ketone XX obtained in 1933 by Hückel from $\Delta^{9:10}$-octalin[48]. This was utilised by Pfau and Plattner[6] who treated it with various Grignard reagents, and by dehydrating and dehydrogenating the products obtained the 4-substituted azulenes. Subsequently they obtained azulene itself by reduction of the keto group, followed by dehydration and dehydrogenation[7].

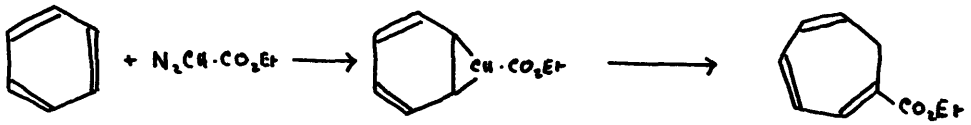


All these synthetic compounds had the intense blue colour characteristic of the natural blue azulenes, and their other properties were similar. It is interesting to notice here that as far back as 1893 Hentschel and Wislicenus[49] had observed a blue colour during the preparation of cyclo-pentanone by distillation of calcium adipate.

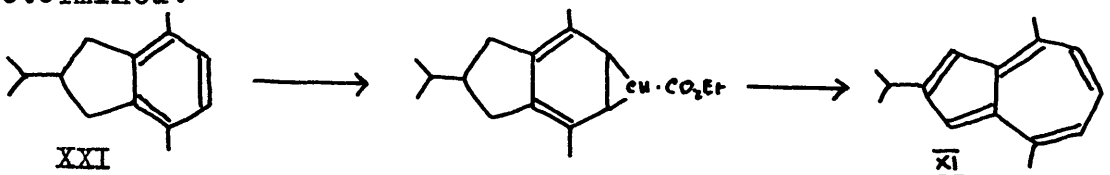
Pfau and Plattner repeated this work and were able to show that the colour was due to the formation of azulene[7]



This method of synthesis is obviously of very limited application, and another was soon devised which has proved of very general use. It is based on the addition of diazo-acetic ester to an aromatic ring, with the production of a 7-membered ring, first described by Buchner in 1885[50].

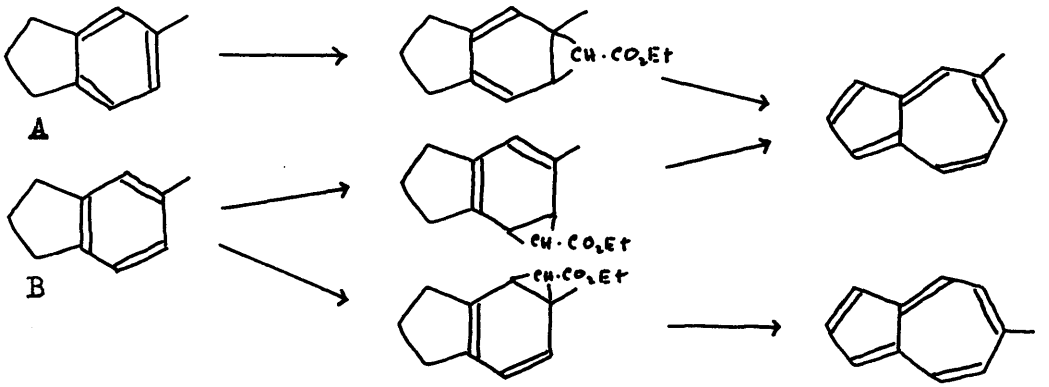


The application of this reaction to suitably substituted indanes has resulted in the synthesis of about 40 azulenes, ranging from the unsubstituted parent hydrocarbon to the polysubstituted 1:3:4:8-tetramethylazulene. The first to be prepared by this method was the natural vetivazulene, which is formed by treating the indane **XXI** with diazoacetic ester, hydrolysing the product to the free acid and then decarboxylating and dehydrogenating this in one operation by heating with palladium charcoal under nitrogen. The intermediate three-membered ring is broken at some point not yet determined.



If the intermediate ester is dehydrogenated directly without hydrolysis, an azulene ester is obtained which may be transformed by standard reactions into other functional derivatives as described in a later section of the present work.

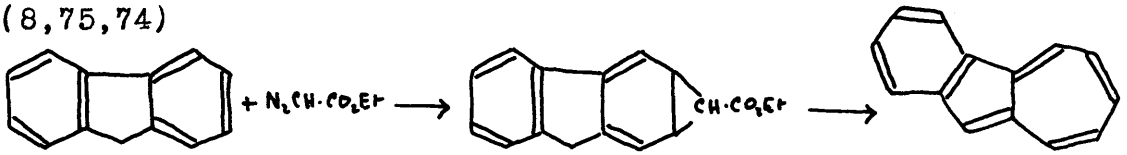
A defect of this synthesis is that in some cases it is not unequivocal, since different products may be obtained according to the double bond to which the diazo-acetic ester adds. The simplest case is that of 5-methylindane, from which 5- or 6-methyl-azulene may result[20,24] :-



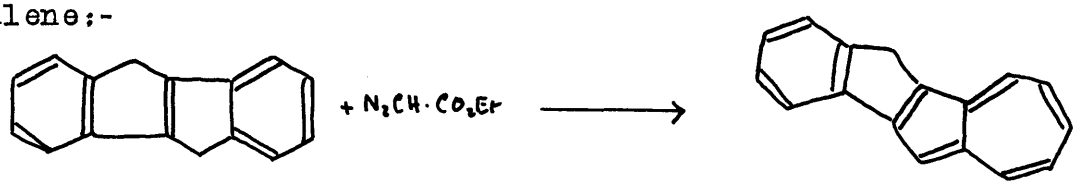
(The possibility of addition to the more severely hindered 7:8, 4:9 or 8:9 double bonds is here neglected.) With poly-substituted indanes the possibilities become more numerous[25]. According to Buchner (loc.cit.) the addition takes place preferentially at unsubstituted C atoms, while Mills and Nixon[61] state that indane itself has predominantly the Kekulé structure shown in A. Whether substituted indanes react according to this structure, however, and what the

steric influence of the alkyl groups may be, cannot be predicted.

The diazo-acetic ester synthesis has also been extended to fluorene, with the production of 1:2-benzazulene (8,75,74)



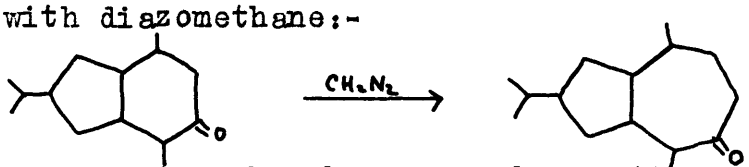
and to an indano-indane to produce the corresponding indano-azulene:-



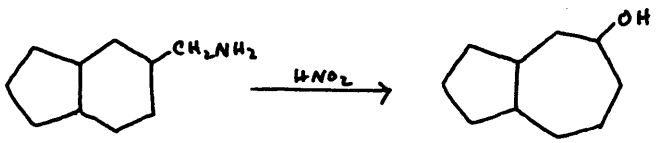
In this latter case only one addition and ring-expansion took place, despite the use of excess diazoacetic ester(85).

Addition of diazoacetic ester to tetrahydroacenaphthene and dehydrogenation of the product has also been reported(81).

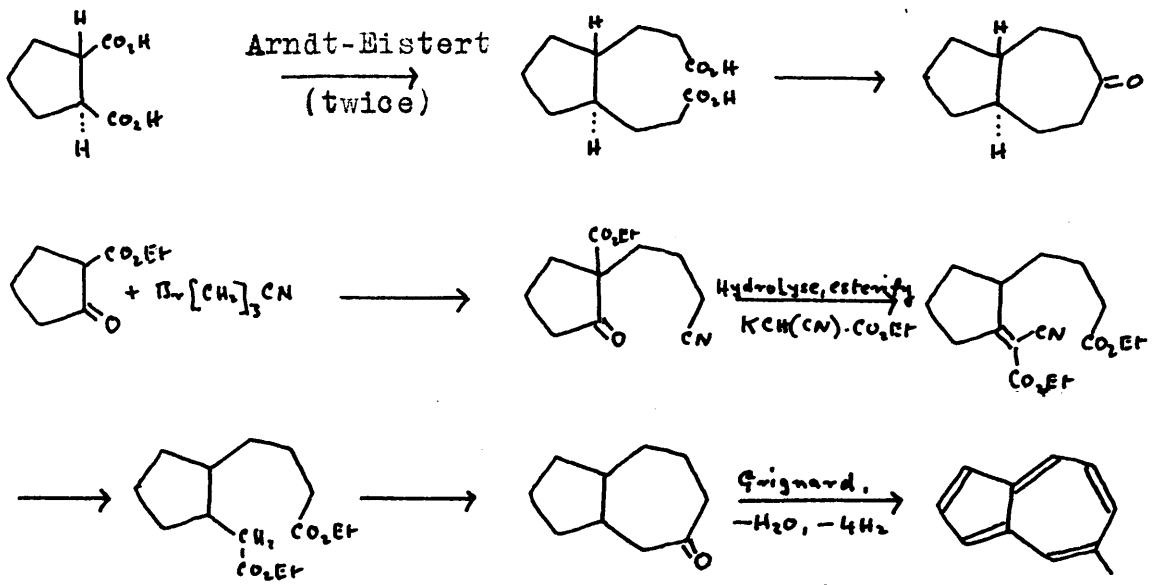
Other methods of synthesis have been used in isolated cases. Thus Coats and Cook(46) devised another synthesis of vetivazulene based on ring expansion of the hexahydroindanone with diazomethane:-



and the same reaction has been used by Plattner for the synthesis of 5-methyl azulene(23). Arnold(21) has made use of the Demjanow rearrangement to achieve ring expansion;-



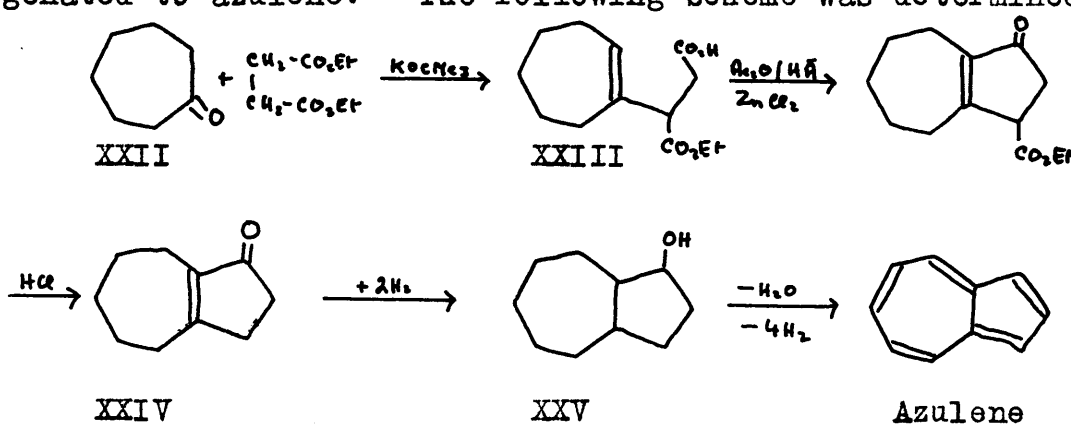
Completely unequivocal syntheses of 5-methyl- and 6-methylazulenes have been achieved by Šorm[22], who started from the 5-membered ring and laboriously built on the 7-membered ring:-



These methods of synthesis have sufficed for the production of a large number of mono- and poly-substituted azulenes in quantities suitable for spectroscopic examination, but for an investigation of the chemical properties of this new quasi-aromatic system much larger quantities are needed, and azulene itself would be preferable to the more highly substituted compounds. The diazoacetic ester method is unsuitable for synthesising large amounts of azulene since

the addition stage goes best with highly substituted indanes and even then gives poor yields, the unreacted starting material having to be re-treated several times. The other ring expansion methods also give poor yields, and in the case of the ring closure method of Šorm, the difficulty would be to obtain a sufficient quantity of starting material.

A more promising method has been suggested by a recent paper by Johnson and co-workers[62]. These workers have developed a new method of building up a five-membered ring, viz., by condensing an appropriate ketone with diethyl succinate (the "Stobbe condensation"[63]) and cyclising the resultant half-ester by refluxing in a solution of acetic anhydride and acetic acid containing a catalytic amount of zinc chloride (a reagent developed by Fieser and Hershberg[64]). It seemed, therefore, that the application of this method to suberone (cycloheptanone) should lead to the required (0:3:5)-bicyclo-decane skeleton, which could then be dehydrogenated to azulene. The following scheme was determined on:-



XXII XXIII XXIV XXV Azulene

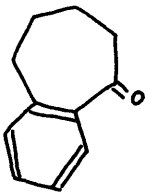
It was also decided to perform the same series of reactions on benzosuberone XXVI in the hope of obtaining benzazulene XXVII as the latter would be useful for comparing the reactivities of the benzene and azulene ring systems. The synthesis of the ketone XXIV by this method was described by Plattner and Büchi[40] shortly after the present work was completed.

1. Azulene series.

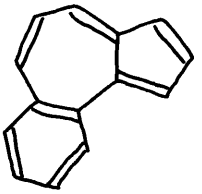
Suberone, the starting material for this synthesis, is most conveniently obtained by treating cyclohexanone with diazomethane according to Kohler, Tishler, Potter and Thomson[65] who form the diazomethane in situ from nitrosomethyl urethane and potassium carbonate; but as nitrosomethyl urethane is not commercially available in large quantities, the original procedure of Mosettig and Burger[66], using ethereal diazomethane, had to be reverted to, despite the inconveniently large volumes involved.

The condensation with ethyl succinate in the presence of potassium tert-butoxide gave an 80% yield of crude half-ester, which by distillation was separated into two components, a liquid and a solid, one of which is presumably XXIII and the other the isomer XXVIII which, by analogy with Stobbe's work (loc.cit.) should be formed in much smaller quantity.

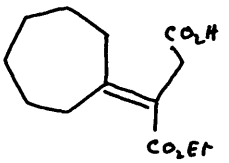
The position of the double bond in these compounds has not been determined with certainty.



XXVI



XXVII



XXVIII

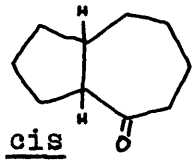
Cyclisation of the crude mixture of half esters with acetic acid, acetic anhydride and a trace of zinc chloride gave, after treatment with water and HCl to decarbethoxylate the intermediate β-keto ester, the unsaturated ketone XXIV in ca 33% overall yield from suberone. This compound, which has a flower-like smell, was readily hydrogenated by Adams' catalyst, but the saturated ketone only was formed. This was later obtained more conveniently by hydrogenation with palladised strontium carbonate. Clemmensen reduction now gave decahydroazulene, and on heating the vapour of this with selenium at a high temperature ($>400^{\circ}$) a blue colour developed, and after several days crystals of azulene formed. The latter were identified by means of the trinitrobenzene compound, which was then decomposed by chromatography to give pure azulene. At lower temperatures ($300-350^{\circ}$) up to 60% of the decahydroazulene was recovered unchanged.

Dehydrogenation of decahydroazulene with sulphur followed by distillation of the product gave a blue fraction, but 70% of the starting material was recovered and much tarry matter was formed.

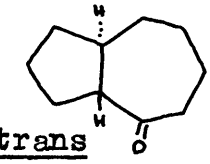
Attempts were made to dehydrogenate ketooctahydro-, ketodecahydro-, and decahydroazulenes by heating with S or Se in sealed tubes. No blue products were isolated.

Treatment of ketooctahydroazulene with aluminium isopropoxide in boiling toluene or xylene gave a mixture of a crystalline carbinol and a lower boiling hydrocarbon, presumably the olefine formed by dehydration. Both of these products could be fairly readily dehydrogenated with selenium, but much resinification took place and the yield of azulene was not sufficient to warrant further investigation.

That the (0:3:5)-bicyclodecane skeleton can exist in cis- and trans- forms has been shown by Hückel's work[48a,b] on the 4-ketodecahydroazulenes and the $\Delta^{4:5}$-octahydroazulenes



cis



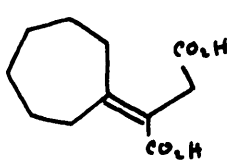
trans

The decahydro azulene obtained here is possibly therefore a mixture of such isomers (but cf also Plattner, Fürst and Jirasek[39]).

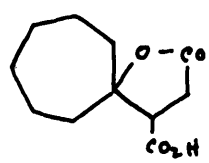
An attempt was also made to prepare 1-phenylazulene

by Grignard reaction of keto-octahydro-azulene with phenyl magnesium bromide followed by dehydrogenation. A blue-green colour was obtained but no trinitrobenzene complex isolated. It has since been shown by Plattner[30], however, that a phenyl group in the 1-position migrates to the 2-position during dehydrogenation and the resulting 2-phenyl-azulene does not form an addition complex with trinitrobenzene.

The suitability for large scale preparations of this synthesis is doubtful. Apart from the dehydrogenation stage, which is necessary to all laboratory syntheses so far devised, the acetic anhydride-zinc chloride cyclisation is unsatisfactory, over 50% of the starting material being converted to a mixture of two acids. These give the same analysis, and the same equivalent (ca 106) is obtained by dissolving them in excess NaOH and back-titrating. Direct titration with alcoholic potash, however, shows that while one is dibasic, with an equivalent of ca 106, the other is monobasic, with an equivalent of ca 212. In addition, the former rapidly decolourises alkaline $KMnO_4$ while the latter does not. These facts point to the formulae XXIX and XXX with which the analyses are in agreement (the position of the double bond in XXIX being, of course, assumed).



XXIX

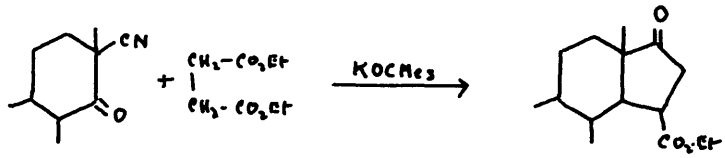


XXX

Attempts to cyclise the mixture, or the pure lactone, by Johnson's method have failed completely, due no doubt to the presence of the extra carboxyl group. Boiling the mixture with acetyl chloride and treating the product (presumably an anhydride) with $SnCl_4$ by the method of Cook and Lawrence[67] failed to produce cyclisation.

Treatment of the mixture of half esters XXIII and XXVIII with anhydrous hydrogen fluoride partly converted it to a liquid anhydride of XXIX; the rest of the material was converted to a mixture of XXIX and XXX. Treatment of the half esters with HF after hydrogenation also failed to produce cyclisation.

Further work by Johnson et al.[68] suggested that better yields might be obtained by condensing ethyl succinate with α-cyano suberone, these authors having carried out the condensation on α-cyano-ketohydrophenanthrenes according to the scheme:



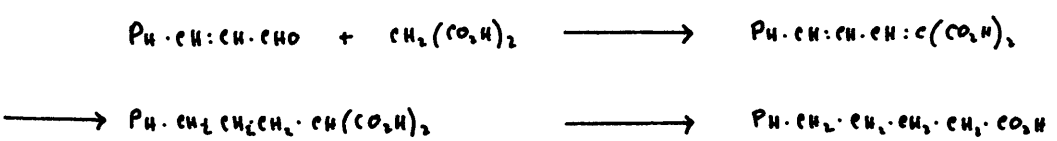
hydrolysis and Dieckmann condensation taking place at the same time. α-cyanosuberone was therefore prepared from hydroxymethylene suberone and hydroxylamine[69,70], but treatment with ethyl succinate and potassium tert-butoxide

did not produce the pink colour characteristic of these condensations and no ketonic products were isolated. Similar treatment of hydroxymethylenesuberone and methoxymethylenesuberone gave a pink colour, but the products appeared to consist mainly of the starting material.

2. Benzazulene series.

Benzosuberone, the starting material in this series, is obtained in 87% yield by the cyclisation of phenylvaleryl chloride with $AlCl_3$ in a large volume of boiling carbon disulphide[71, cf.72]. About 14% of benzosuberone is obtained by treating the chloride with HF, but the free acid is not cyclised in this way.

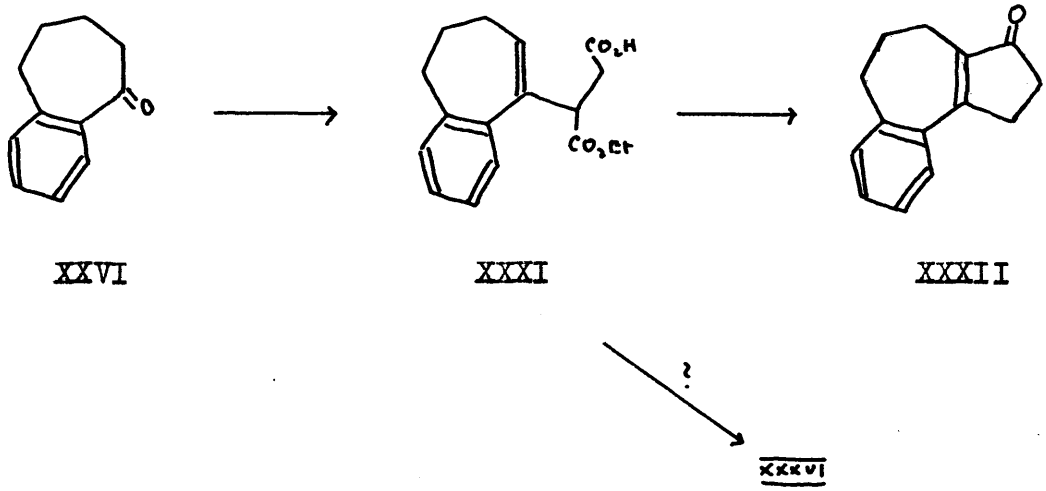
Phenylvaleric acid has been prepared in 85% yield from cinnamaldehyde by condensation with malonic acid in presence of quinoline, reduction of the cinnamylidene-malonic acid with Raney Ni/Al alloy in NaOH solution and decarboxylation of the crude product by heating in vac. in the presence of copper powder.



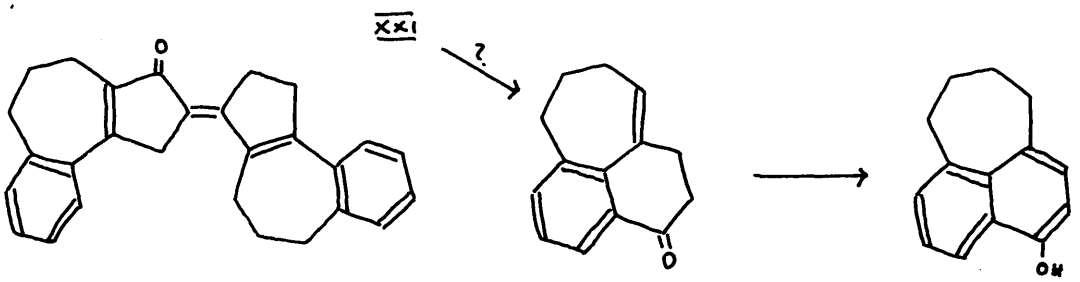
This represents a considerable advance on previous work, in which only 27% overall yields have been obtained[73].

Another method used was to hydrogenate cinnamylidenemalonic acid in cellosolve solution over palladised strontium carbonate and decarboxylate by boiling the solution. The decarboxylation of cinnamylidenemalonic acid by heating in pyridine or quinoline was found to be unsatisfactory owing to the formation of by-products and tars.

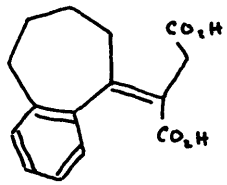
Condensation of benzosuberone with ethyl succinate by the same method as before gave 67% of crude acidic material which was refluxed with Ac_2O / $H\bar{A}$ / $ZnCl_2$ solution. 28% of a neutral, ketonic oil was obtained, the remainder of the material giving an acidic product. The neutral material was separated by distillation into a solid ketone m.p. 59-60° whose <u>semicarbazone</u> analysed for the required <u>ketohydrobenzazulene</u> XXXII, and a small amount of a solid m.p. 199-201° which gave a 2:4-dinitrophenylhydrazone only on long standing. This did not analyse in agreement with either of the structures XXXVI or XXXIII.



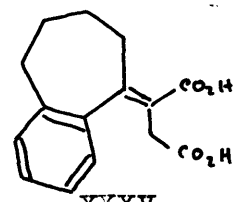
XXVI XXXI XXXII



XXXIII XXXVI XXXVII



XXXIV

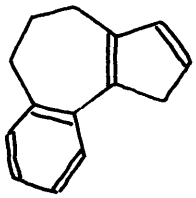


XXXV

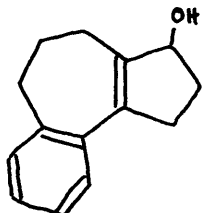
An attempt to dehydrogenate the ketone XXXII by heating with Se in a sealed tube gave no highly coloured product.

The acids obtained during the cyclisation of XXXI were extracted with $NaHCO_3$ and the residue was observed to have a phenolic smell, possibly due to the presence of XXXVII, though an ethereal solution gave no colouration with aq. $FeCl_3$.

The mixture of acids has not been separated, but may contain several isomers, e.g., XXXIV and XXXV as well as lactones analogous to XXX.



XXXVIII



XXXIX

The ketone XXXII was reduced with aluminium isopropoxide in boiling toluene and the product separated into three fractions by distillation: a fairly mobile oil, b.p. 95°/0.1 mm., a more viscous oil, b.p. 120°/0.1 mm. and crystals, m.p. 123-124°. From the analytical results the first of these appears to be mainly the hydrocarbon XXXVIII, and the second a mixture of this hydrocarbon with the carbinol XXXIX. The hydrocarbon was heated with palladium black under nitrogen, but the material turned tarry and gave no highly coloured products. The tricyclic ketone was also hydrogenated over PtO_2 (Adams' catalyst) and Raney nickel. The former catalyst gave a mixture of saturated carbinol and hydrocarbon, but the latter gave a more homogeneous product, apparently mainly carbinol. This was dehydrogenated with selenium at ca 400°, but although H_2Se was evolved, the product was a tar. Palladium and sulphur dehydrogenations were also tried without success.

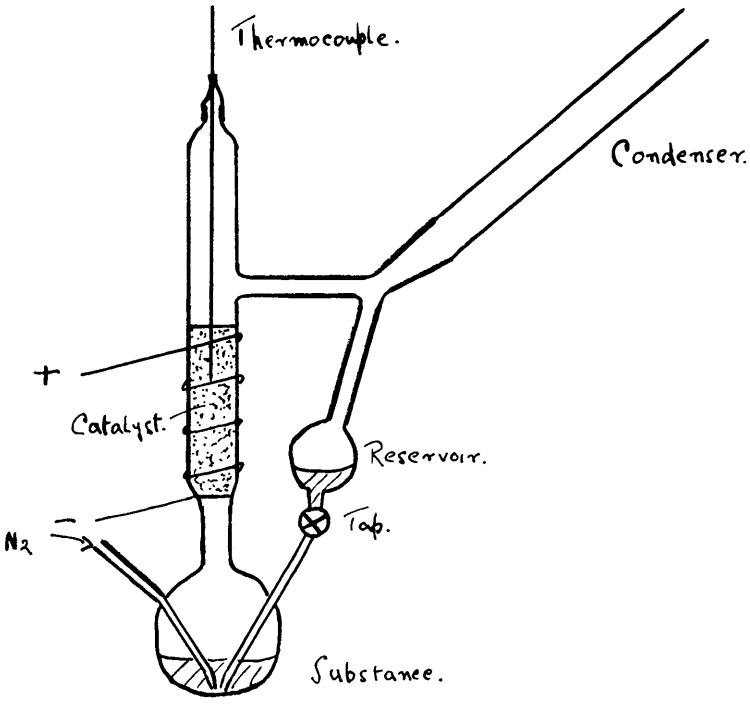
It may be noted that Cook, McGinnis and Mitchell were also unsuccessful in dehydrogenating a similar precursor to 5:6-benzazulene[82].

The limiting factor in these syntheses then, is the final dehydrogenation of a relatively saturated structure which gives yields of ca 1% or less. The diazoacetic ester method is superior in this respect since three double bonds

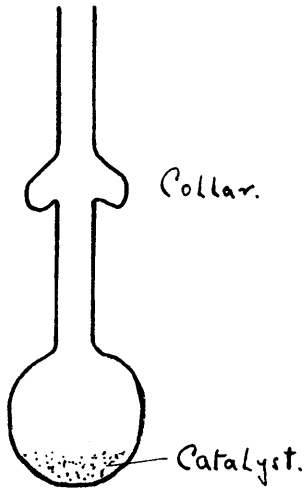
are present before dehydrogenation, but even here the yields are seldom more than 5-10% and often much less, especially if decarboxylation is taking place simultaneously. If the material to be dehydrogenated is saturated, as e.g., decahydroazulene, the reaction requires drastic conditions, but the unreacted starting material is relatively stable and can be recovered : whereas if it is unsaturated there is a considerable loss from resinification, and the time of contact with the catalyst must be kept to a minimum. This applies especially in the case of azulene itself which is not so stable as its higher homologues and is quite readily isomerised to naphthalene at temperatures around 300°[35,36]. In an attempt to overcome these difficulties an apparatus was constructed for dehydrogenation in the vapour phase and subsequent removal of the products from the reaction. This was based on an apparatus described by Ruzicka[78] and is illustrated in the accompanying diagram A. The catalyst can be heated electrically to any desired temperature, and the rate of flow of the substrate is determined by the nitrogen stream. The vapour is then condensed and collected in a reservoir and can be returned periodically to the boiling flask via the tap.

This apparatus was used for the dehydrogenation of decahydroazulene over a 10% palladium charcoal catalyst, but

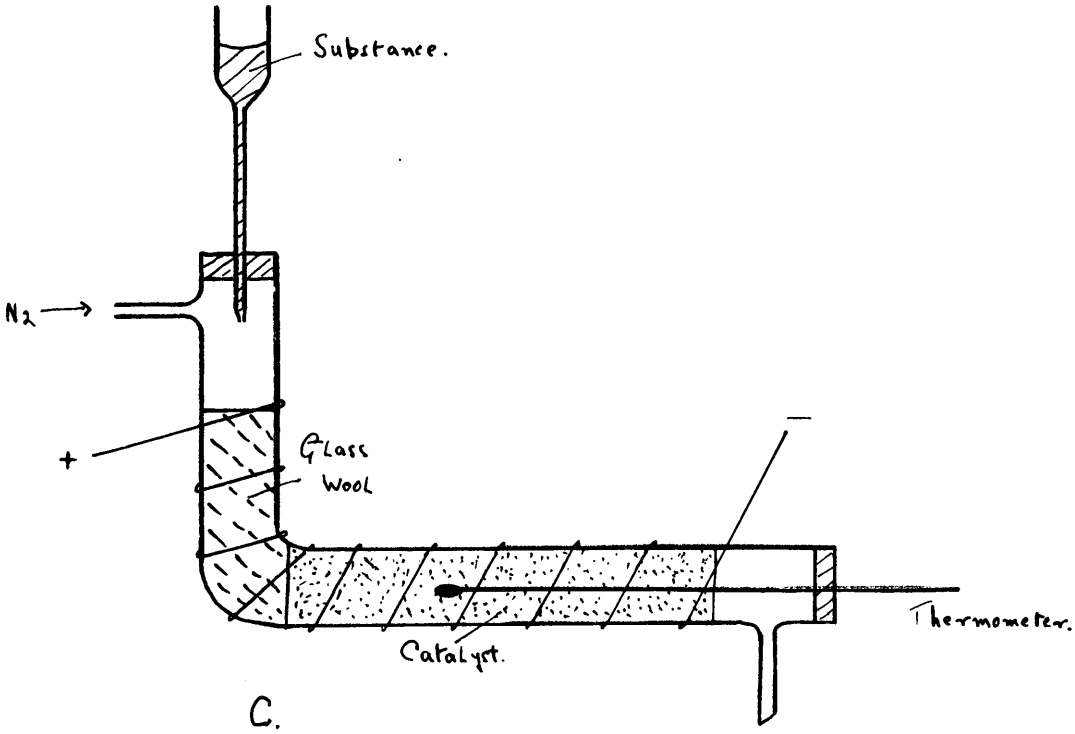
Dehydrogenation Apparatus



A.



B.

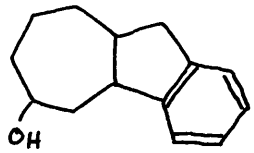


C.

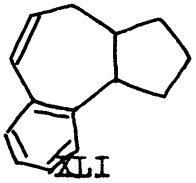
some of the azulene formed appeared to decompose in the boiling flask, and at high temperatures (ca 400°) the formation of naphthalene was noted. The tricyclic carbinol obtained by Raney nickel reduction of the ketone XXXII was also vapourised in this apparatus at ca 430°, but no coloured products were obtained.

The apparatus used till recently by Plattner and his collaborators in Zürich for the dehydrogenation of diazoacetic ester adducts was a simple collar flask as shown in diagram B. The substrate is dropped on to the heated catalyst from a fine pipette and the product allowed to condense in the collar, from which it can be removed periodically with a pipette, the azulene extracted with phosphoric acid, and the residue re-treated. This has now been replaced by the apparatus shown in diagram C, which was used for the preparation of 2-methylazulene-6-carboxylic ester as described below. The catalyst is contained in the horizontal portion of the tube, the vertical part being loosely packed with glass wool in order to ensure the vaporisation of the material before it reaches the catalyst. Here again the azulene is extracted from the product before re-cycling, which may be repeated several times. Recently (April 1949) Nunn and Rapson[74] have described an apparatus for vapour phase dehydrogenation in vacuo which has apparently been

very successful in the production of 1:2-benzazulene from the carbinol XL which could not be dehydrogenated by other means.



XL



XLI

A still more recent paper (May 1949) by these authors[80] describes the dehydrogenation of XLI to 4:5-benzazulene XXVII, which however, was found to be unstable and has only been isolated as the TNT or trinitrobenzene complexes.

A full chemical investigation of the azulene structure still awaits the discovery of a suitable synthetic method. The most hopeful large scale process so far reported is the polymerisation of acetylene with a nickel cyanide catalyst which was developed in Germany during the war for the synthesis of cyclooctatetraene[52]. Azulene is produced as a by product in this reaction, and is believed to have been obtained in fairly large quantities, but since it involves handling acetylene at 15 atm. pressure it is not suitable for ordinary laboratory use.

During a few months spent in the laboratories of Professor L. Ruzicka and Professor P.A. Plattner at the Eidgenössische Technische Hochschule, Zürich, some new compounds of the azulene series were prepared by utilising the

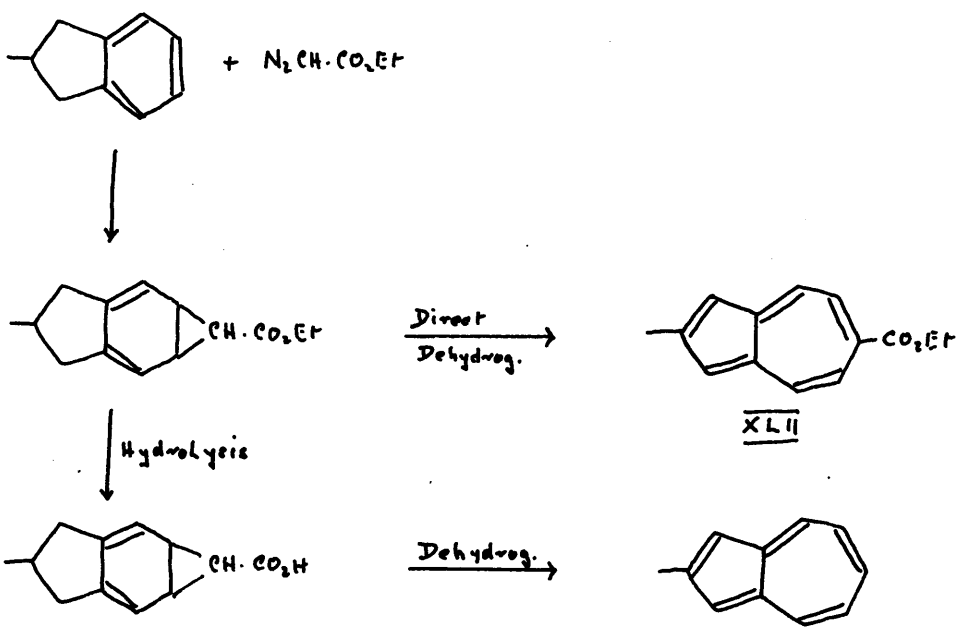
comparatively readily available 2-methyl-6-carbethoxyazulene.

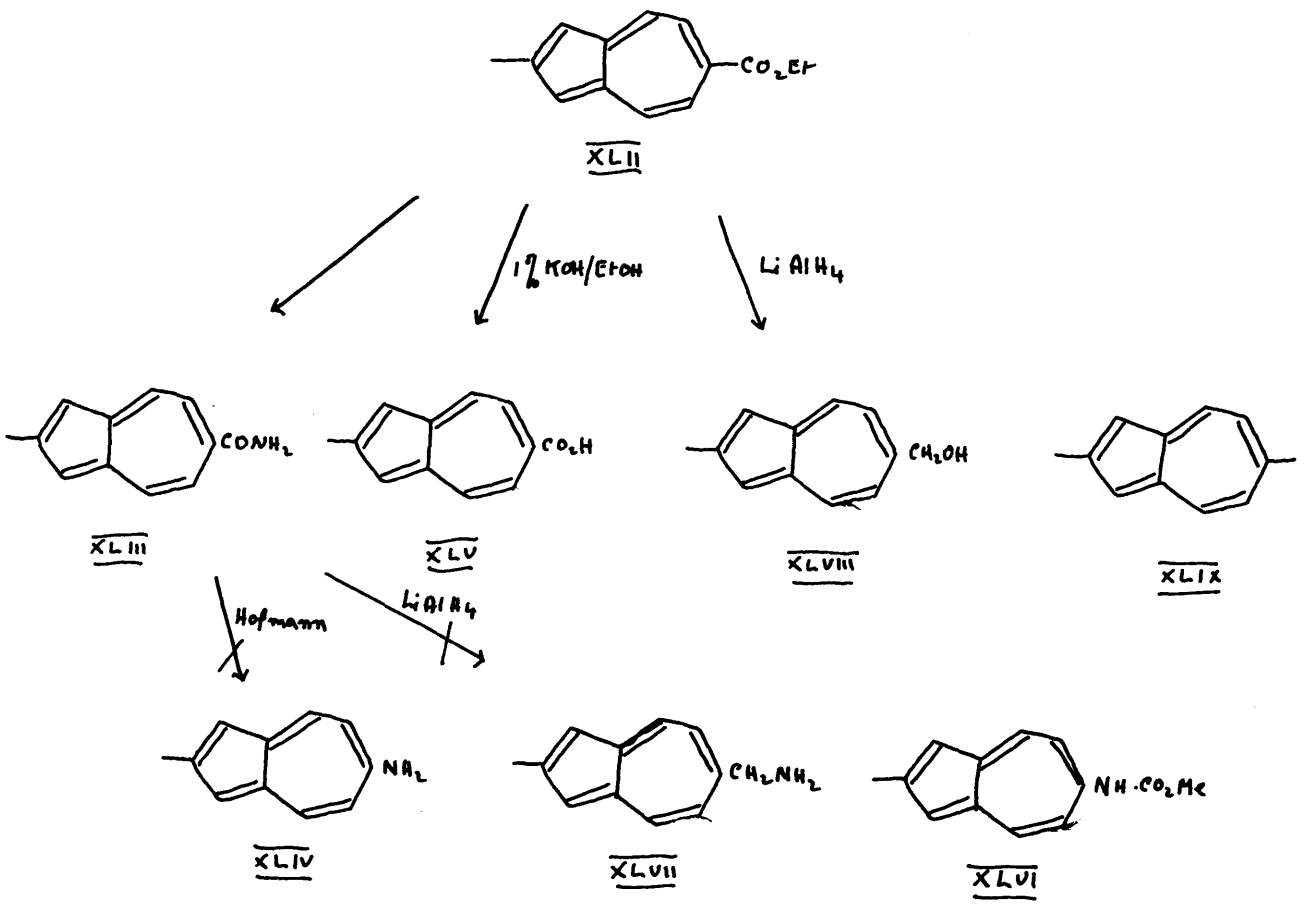
This ester (XLII) was made by treating 2-methylindane with diazoacetic ester and dehydrogenating the medium boiling fraction of the product with 10% palladium charcoal in the vapour phase apparatus previously mentioned (diagram C). This process gave overall yields of ca 7% from 2-methylindane. A specimen of 2-methylazulene for X-ray and infra-red measurements was also prepared by dehydrogenating the addition product after hydrolysis. The yield in this case was ca 2.5% from 2-methylindane.

It was first of all desired to prepare the amide XLIII and attempt its degradation by the Hofmann reaction to the amine XLIV, a type of compound hitherto unknown in the azulene series. The ester was therefore hydrolysed with 1% alcoholic potash to the free acid XLV, which was then treated with thionyl chloride and ammonia. No amide was obtained however, the principal product being a green amorphous compound soluble only in alcohols. Next the ester was treated with alcoholic ammonia in the cold, but after standing for a week and then refluxing, no amide was obtained. Treatment of the ester at 190° for 23 hours with ammonia gas in 96% ethanol containing a few drops of ethylene glycol gave the amide in ca 76% yield, together with a little of the free acid. It is interesting to note that when 99% alcohol was substituted,

very little amide was formed and the ester was recovered unchanged.

The Hofmann reaction on the amide XLIII was attempted using sodium hypochlorite, as it was thought that hypobromite might lead to halogenation of the azulene nucleus. Hypochlorite was found to be without action on guajazulene under the conditions of the reaction. The amide was kept for 2 hours at 35° with aqueous NaOH + NaOCl, but was recovered largely unchanged. It was next sought to prepare the urethane XLVI by carrying out the reaction in methanol, but hydrolysis resulted and much of the amide was converted to the free acid. The rest of the material was not acid soluble.





Owing to shortage of time the Hofmann reaction was not pursued, and attempts were made to reduce the amide with lithium aluminium hydride to obtain the amine XLVII, but these were unsuccessful, only a trace of pink acid soluble material being obtained.

2-Methyl-6-carbethoxyazulene was also treated with lithium aluminium hydride and readily gave a crystalline, violet alcohol XLVIII. A similar violet compound was also produced by reduction of the free acid XLV with $LiAlH_4$, but

this material was not characterised. During the reduction of the ester a trace of pure blue material, not absorbed on the chromatogram, and with a complex spectrum suggesting 2:6-dimethylazulene XLIX, was obtained.

Experimental

1. Azulene Series.

Suberone

(1) Method of Mosettig and Burger[66].

480 g. cyclohexanone dissolved in 600 ml. methanol was added to 8.75 l. of an ethereal solution containing 269 g. diazomethane. (The latter was prepared from nitrosomethylurea in the usual way and estimated by treating a sample with excess glacial acetic acid and measuring the nitrogen given off). The mixture was cooled initially to 0° but as only a slow reaction set in it was allowed to stand at room temperature for two weeks, after which it became almost colourless. The ether and methanol were distilled off and the residue fractionated, during which 15 g. of a white, hygroscopic solid m. 128-35° separated and was filtered off (polymethylene: cf. Mosettig and Burger loc.cit.). The separation was found to be unsatisfactory owing to the presence of cyclo-octanone and other by products so the fractions were re-combined and treated with sodium bisulphite solution. After washing with ether the compound was steam distilled with Na_2CO_3, the distillate dried and re-distilled in vac. 155 g., b. 73-77°/23 mm. (28%). It was identified as suberone by

means of the semicarbazone which crystallises from alcohol in shining plates m. 162-163.5°, while cyclohexanone semicarbazone crystallises in effloresoent needles m. 166-167.5° which are easily distinguished. Mixed m.p. 156-159°. The residues from the bisulphite extractions were treated with semicarbazide hydrochloride and pyridine in aq. alcohol and gave 3.01 g. of a semicarbazone m. 161-163°, mixed with suberone semicz. m. 151-154°, mixed with cyclohexanone semicz. m. 150-155° (cyclo-octanone semicz. m. 163-164.5°).

The residues from this treatment were distilled and gave 138 g., b. 140°/23 mm. of a yellow oil which turned deep crimson on standing, and 20.2 g., b. 160-180°/23 mm. of a thick orange oil. These correspond with the by products found by Kohler[65].

1). Δ^1-cyclohexenyl carbinol b. 92-94°/15 mm.

2). Di-cyclohexyldioxane (?) b. 147.5-148°/11 mm.

(ii) Method of Kohler, Tishler, Potter and Thomson[65].

To a stirred mixture of 10 ml. cyclohexanone, 10 ml. abs. methanol and 50 mg. anhydr. Na_2CO_3 was added 1 ml. nitrosomethylurethane. After an induction period of about 30 minutes, reaction commenced, as evidenced by a rise in temperature and evolution of nitrogen. The temperature was kept at 20-25° by ice water and the remainder of the 12 g.

nitrosomethylurethane added over two hours.

The mixture was stirred for a further hour and left overnight. After removing the alcohol the ketone was purified through the bisulphite compound, and redistilled. Yield, 5 g. b. 178-182°/760 mm. (45%).

β-carbethoxy-β-Δ'-suberenyl propionic acid XXIII. (Stobbe condensation on suberone.)

50 g. suberone and 120 g. ethyl succinate were added to a chilled solution of 25 g. potassium in 500 ml. t-butyl alcohol, and the mixture, which developed a deep pink colour, was refluxed 40 minutes, in an atmosphere of nitrogen. After cooling and acidifying with HCl (1:5) the alcohol was removed under reduced pressure, the oil extracted with ether, which, after washing, was extracted with Na_2CO_3 solution. This was washed with ether and acidified, yielding 98 g. crude acidic material, which on distillation gave the following fractions:-

1) b. 160°/1.5 mm; ca 10 ml: solidified to small white needles.

2) b. 180°/1.5 mm. an oil.

These fractions (isomeric) were not separated: total yield 72.5 g. (68%).

A small amount of the solid was collected and crystallised from petroleum: clusters of white needles, m.p. 68-70°.

(Found: C = 65.1%, H = 8.2%; $C_{13}H_{20}O_4$ requires C = 65.0%, H = 8.3%).

Examination of the residues after the alkaline extraction revealed some unchanged suberone which on re-treatment gave a further quantity of half ester, bringing the total yield up to 80%.

1-keto- $\Delta^{9;10}$-octahydroazulene XXIV.

13.6 g. of the above mixture of isomers was dissolved in 155 ml. acetic anhydride and 78 ml. glacial acetic acid containing 20 mg. fused zinc chloride per ml. This was refluxed for 3.1/2 hours in a current of nitrogen. 155 ml. water was then added followed by 62 ml. conc. HCl and the solution refluxed a further 45 minutes to hydrolyse the intermediate β-keto ester. The solvent was distilled off in vac. and the residue digested with 200 ml. 5% KOH for 1/2 hour on the steam bath. From this by ether extraction was obtained 2.1 g. ketone, b. 62-64°/0.1 mm. (25%). After purification through the semicarbazone (m. 235-236° decomp.; Found C = 63.8%; H = 8.1%; N = 20.4%; $C_{11}H_{17}ON_3$ requires C = 63.8%; H = 8.2%; N = 20.3%). This was obtained as a colourless oil, b. 58-60°/0.1 mm. $n_D^{11.5°}$ = 1.5275. (Found C = 79.9%; H = 9.2%; $C_{10}H_{14}O$ requires C = 80.0%; H = 9.3%).

During the cyclisation considerable darkening occurred even when "Analar" reagents were used. The alkaline extracts on acidification gave 1.52 g. of a brownish white solid m. 157-160°.

On a larger scale 57.5 g. material was treated as above: a deep purple colour developed on adding the HCl, and some solid precipitated during the removal of the solvent. 8.5 g. ketone (24%) was obtained and a total of 28.2 g. acidic solid, including two lots of material precipitated as above, and a third obtained by alkali extraction. These had m.p. 168-170°, 184-186° and 174-175° (sint. 157°) respectively and on purification by repeated crystallisation from dilute acetic acid were found to contain two pure compounds only: (A) strong white needles m. 171° (Found: C = 62.3%; H = 7.2%) and (B) small white plates m. 184-186° (Found: C = 62.3%; H = 7.4%). Mixed m.p. 158-161°. The former decolourised $KMnO_4$ rapidly, the latter did not.

Titration of acid by products.

71 mg. A was dissolved in 10 ml. 0.1 N NaOH and titrated with 0.1 N HCl using phenolphthalein as indicator.

Titration = 2.4 ml.

∴ 71 mg. A = 7.6 ml. 0.1 N NaOH

i.e. equiv. of A = $\frac{71}{1000} \times \frac{10,000}{7.6}$ = 93.

B was titrated similarly: 77.5 mg. = 8.0 ml. 0.1 N NaOH

i.e. equiv. of B = 97.

Direct titrations were then carried out in alcoholic solution using alcoholic KOH with phenolphthalein as indicator.

10 ml. 0.1 N HCl = 12.1 ml. KOH

81 mg. A = 9.2 ml. KOH

$$\therefore \text{ equiv. of A} = \frac{81}{1000} \times \frac{12.1 \times 1000}{9.2} = \underline{106.5}$$

75 mg. B = 5.1 ml. KOH

$$\therefore \text{ equiv. of B} = \frac{75}{1000} \times \frac{12.1 \times 1000}{5.1} = \underline{211}$$

(XXIX ($C_{11}H_{16}O_4$) requires C = 62.3%; H = 7.6%; equiv. = 106;
XXX ($C_{11}H_{16}O_4$) requires C = 62.3%; H = 7.6%; equiv. = 212.)

Subsequent preparations of the ketone were carried out without purifying the intermediate half ester, and yields up to 33% from suberone were obtained.

1-Keto-decahydroazulene.

1.34 g. XXIV was shaken with hydrogen in presence of Adams' platinum catalyst in ethanol for 5 hours after which the absorption was virtually complete. The product gave a semicarbazone m. 229-230° decomp. (Found C = 63.3%; H = 8.9%; N = 20.0%: $C_{11}H_{19}ON_3$ requires C = 63.2%; H = 9.1%; N = 20.1%).

Using $Pd/SrCO_3$ the reduction was complete in 2.1/4 hours, the same product being formed.

Decahydroazulene.

0.95 g. 1-keto-decahydroazulene was reduced by Clemmensen's method using 2 g. amalgamated zinc and 6 ml. HCl (7 parts conc. HCl: 3 parts H_2O) with a few drops of glacial acetic acid. After 12 hours' refluxing 25% of the material was unchanged. After 30 hours' refluxing a 60% yield of decahydroazulene b. 192° was obtained, 10% of the ketone being recovered.

Dehydrogenation of decahydroazulene.

1.16 g. decahydroazulene was refluxed with 3.5 g. Se at 360° for 4 days using a long necked flask with internal condenser, the temperature being allowed to rise finally to >400°. Blue crystals formed on the condenser and on extracting with petroleum a deep blue solution was obtained. This was extracted with phosphoric acid (s.g. 1.75), the extract washed with petroleum, diluted and extracted with ether. On evaporation of the latter a blue solid remained. This was taken up in 5 ml. alcohol and warmed with 100 mg. s-trinitrobenzene. On cooling fine brown needles were deposited which on recrystallisation from alcohol gave 56 mg. azulene trinitrobenzolate m. 165-167° (lit. 166.5-167.5°). This was dissolved in 10 ml. cyclohexane/benzene (1:1) and passed through a 5 cm. column of alumina. The azulene was washed through with 20 ml. cyclohexane and the resulting deep

blue solution distilled (through a short column to prevent volatilisation of azulene). Bright blue crystals of azulene remained m. 85-89° (micro apparatus) (lit. 98-99°).

1 g. hydrocarbon and 0.2 g. sulphur (16% of theory) were heated in a long necked flask to 210° when reaction set in and H_2S was evolved. After 12 hours at 210-240° the evolution of H_2S appeared to have stopped and the dark, brown tarry product was distilled. 0.71 g. hydrocarbon was recovered, followed by a drop of a bright dobalt blue liquid. The colour could be extracted with conc. phosphoric acid and regenerated by dilution with water.

Heating with selenium at 360° for 55 hours gave a deeper blue product with no tarry matter, but 63% of the hydrocarbon was recovered and the amount of azulene present was too small to identify. Treatment with a few mg. s-trinitrobenzene in alcohol gave some black needles m. ca 110° decomp.

Heating decahydroazulene or XXIV with selenium in sealed tubes at 300-350° for periods up to 52 hours gave no blue products.

Ponndorf reduction of ketooctahydroazulene XXIV.

The ketone XXIV (2.75 g.) was refluxed for 4 hours with aluminium isopropoxide (re-distilled, 8 g.) in xylene (50 ml.). After washing with dil. HCl and evaporating the

solvent, the product was distilled, giving two fractions:- (1) mobile b. 80°/17 mm. (0.37 g.) and (2) viscous b. ca 140°/1 mm. (1.82 g.). The latter was re-distilled b. 148°/1 mm., and was recrystallised from aq. alcohol to give fine white needles m.p. 41-43°. The analysis of these was not satisfactory. (Found: C = 81.69, 81.82%; H = 9.07, 9.26%: $C_{10}H_{16}O$ req. C = 78.90; H, 10.60%).

The use of benzene or toluene as solvents in an attempt to prevent dehydration of the carbinol lowered the yield considerably, much ketone being recovered.

The carbinol (0.37 g.) was treated with 3:5-dinitrobenzoyl chloride (1.5 g.) in benzene with the addition of a few drops of pyridine. After boiling for a few minutes and cooling, ether was added, the precipitate filtered, washed with dilute acid, alkali and water. This material (m.p. ca 196°) did not crystallise well and was therefore treated with α-naphthylamine in ether. A red complex was formed which crystallised in small red needles from methanol, m.p. 197-198°. The analysis of this could not be interpreted. (Found: C = 57.67%; H = 3.73%; N = 12.05%).

Both Ponndorf products were dehydrogenated with Se at 250-330° (3-4 hours) and with palladium charcoal at ca 250-340° (45 minutes under N_2). Deep blue distillates were obtained in all cases from which the azulene could be extracted

with phosphoric acid and converted to the trinitrobenzene complex, but the yields were small and much tar was formed.

Dehydrogenation of decahydroazulene in the vapour phase apparatus (diagram A) using 10% palladium charcoal at ca 430° gave small amounts of azulene together with some naphthalene (identified as the picrate, m.p. and mixed m.p.).

Grignard reaction on keto-octahydroazulene.

Phenyl magnesium bromide (50% excess) was prepared from 3.93 g. bromobenzene and 0.61 g. magnesium with the aid of a little methyl magnesium iodide. To this was added, dropwise, 2.5 g. keto-octahydroazulene in dry ether. A yellow gummy solid precipitated and after standing overnight the mixture was refluxed 30 minutes and the complex decomposed with ice and dil. H_2SO_4. The product, obtained by ether extraction, consisted of 3.29 g. thick greenish brown oil, which did not distil at water bath temperature under 18 mm. pressure.

This was heated under reflux with 3.3 g. selenium at 360° for 16 hours. Some low boiling material (ca 200°) appeared to be present and also some moisture (from dehydration of the carbinol ?) but the main body of the liquid started to boil at ca 310° and H_2Se was evolved soon after. On distilling the product, some yellow oil distilled at ca 140°/18 mm., then a drop of blue liquid appeared at ca 220°

(air bath temperature) followed by some thick green liquid. Extraction of the colouring matters with conc. H_3PO_4 gave 72 mg. green oil from which, however, no trinitrobenzene compound could be obtained.

Attempted cyclisation of XXIII with hydrogen fluoride.

5 g. crude product from the Stobbe condensation on suberone was placed in a platinum crucible which was then filled with 10 ml. anhydrous hydrogen fluoride and left for 5 hours. The hydrogen fluoride was then allowed to evaporate, the residue taken up in ether and washed with water and with Na_2CO_3 solution. The alkaline extract yielded 1.19 g. of an acid sint. 160° m. 166-167° which proved to be a mixture of XXIX and XXX, while evaporation of the ether layer gave 2.62 g. reddish brown oil b. 158-166°/0.8 mm. The latter was readily hydrolysed by acid or alkali, or by standing for some time to the acid described above. This acid was identical with XXIX - mixed m.p. 171°.

Hydrogenation of XXIII.

10 g. crude Stobbe condensation product was hydrogenated over $Pd/SrCO_3$. Hydrogen was rapidly absorbed to give a colourless oil which was used without further purification.

2 g. of this material was treated with hydrogen fluoride as above, and another portion with $H\bar{A}c/Ac_2O/ZnCl_2$.

The products have not been fully characterised, but no ketonic material has been isolated.

Attempted cyclisation of the mixture of XXIX and XXX.

1). With $SnCl_4$.

1 g. of the crude mixture of acids was refluxed 30 minutes in 5 ml. acetyl chloride. After removal of the excess acetyl chloride in vac. a thick brown oil remained which partly solidified. This was treated with 1.25 g. stannic chloride in carbon disulphide by the method of Cook and Lawrence[67]. After decomposing the complex with ice and extracting with carbon disulphide, evaporation of the extract gave 0.33 g. of an oil which crystallised after several months, giving long needles m. 71-72°, which had no ketonic properties. (Found: C, 64.50, H, 7.96%).

2). With $H\bar{A}/Ac_2O/ZnCl_2$.

1.17 g. acid was refluxed 4½ hours under nitrogen with 19 ml. Ac_2O, 6 ml. glacial. $H\bar{A}$ and 6 ml. $H\bar{A}/ZnCl_2$ (20 mg./ ml). 0.97 g. acid was recovered unchanged.

This was repeated using the pure lactone XXX with similar result.

Hydroxymethylene suberone (Wallach, Steindorff[76]).

(i). NaOMe method.

2.1 g. Na was dissolved in 30 ml. methanol and the solution evaporated under reduced pressure. The NaOMe was powdered and 6.65 g. ethyl formate in 45 ml. sodium dried

benzene added, followed by 5 g. suberone in 50 ml. dry benzene, with cooling and swirling. The flask was then evacuated, filled with N_2 and left overnight. After hydrolysis with cold water, the organic layer was separated and washed with dilute NaOH and the combined aqueous layers acidified. The precipitated oil was extracted with ether, dried and distilled. Yield, 4.85 g. b. 90-94°/18 mm. (78%).

(ii). Atomised Na method.

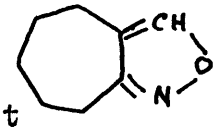
2 g. Na was atomised in boiling toluene, the toluene decanted and the Na covered with dry ether. 6.5 g. ethyl formate in ether was then added, followed with cooling in ice, by 4.71 g. suberone in ether. Reaction set in at once, as evidenced by effervescence and the formation of a salmon pink precipitate. After standing 2 hours in ice water, the mixture was allowed to stand overnight at room temperature and was then hydrolysed with moist ether and worked up as before. Yield, 5.01 g. (85%) colourless oil. b. 104-110°/23 mm. (lit. b. 100°/10 mm.)

α-cyano suberone. (Ziegler et al.[77]).

4.32 g. hydroxymethylene suberone was stirred with 4.3 g. powdered hydroxylamine hydrochloride (100% excess) in 50 ml. glacial acetic acid at 70-80° for 8 hours. On cooling this was filtered from excess $NH_2.OH.HCl$ and the

solvent removed in vac. The orange residue was washed with water and extracted with ether, the extract being washed with $NaHCO_3$ solution to remove unchanged starting material. The mixture of isomeric isoxazoles obtained by evaporation of this extract was dissolved in 50 ml. dry ether and 10 ml. of a concentrated solution of sodium in methanol added. A white precipitate formed and after 1 hour this was hydrolysed with cold water, the ether separated and the aqueous layer saturated with salt and acidified. The precipitated oil was extracted with ether, dried and distilled. Yield, 1.65 g. (39%) pale yellow oil, b. 140-142°/17 mm. (lit. 140-141°/12 mm.). This gradually deposited a solid polymer on standing.

The stable <u>β γ-suberanyl isoxazole</u>



was recovered from the ether layer by treatment with a saturated alcoholic solution of mercuric chloride, when the white crystalline double salt precipitated (m. <u>ca</u> 98-100°). It was decomposed by dissolving in HCl, precipitating the Hg with NaOH and removing the isoxazole by steam distillation. The compound was thus obtained as a colourless liquid b. 50-52°/0.2 mm. (Found: C = 69.5%; H = 7.6%; N = 10.0%: $C_8H_{11}ON$ requires C = 70.1%; H = 8.0%; N = 10.2%).

Condensation of α-cyano suberone and ethyl succinate.

1.71 g. α-cyano suberone was mixed with 3.3 g. (50% excess) ethyl succinate and added to a chilled solution of 0.55 g. potassium in 10 ml. t-butyl alcohol. A white precipitate formed and the material was refluxed under N_2 for 1 hour. After working up in the usual way some gummy material was obtained from which some starting material was recovered by alkali extraction. No ketonic products were isolated.

Condensation of hydroxymethylene-suberone and ethyl succinate.

0.5 g. hydroxymethylene-suberone was treated as above with 1 g. ethyl succinate and 0.3 g. potassium in 10 ml. t-butyl alcohol. A deep red colour developed, but the products apparently consisted mainly of starting materials and polymers. The use of methoxymethylene-suberone (b. 116-120°/13 mm., from hydroxymethylene-suberone with diazomethane in presence of methanol) gave similar results.

2. Benzazulene series.

δ-Phenylvaleric acid.

Cinnamic aldehyde (100 g.), malonic acid (80 g.) and quinoline (98 g.) were mixed and warmed to a clear solution on the water bath. A few drops of piperidine were then added and the mixture allowed to stand 4 days in the cold.

It was then warmed 2 hours on the water bath, dissolved in NaOH (270 g. in 2 l. water) and the quinoline extracted with ether. After distilling off the dissolved ether, the solution was raised to boiling point and Raney Ni/Al alloy (160 g.) added with vigorous stirring during ¾ hour (sec. octyl alcohol used to reduce frothing). The mixture was then stirred at 90° for ½ hour and filtered. The hot filtrate was now siphoned slowly into hot sulphuric acid (600 ml. conc. - 1 l. water) with vigorous stirring. On cooling, the precipitated oil was separated, dissolved in ether and washed free from aluminium salts. After evaporation of the ether it was then heated under vac. (ca 20 mm.) in presence of copper powder, for 2 hours at 140-180°. The resulting phenylvaleric acid was crystallised from petroleum (40-60°), m.p. 59-60°. Yield, 115 g. (85% overall).

In other preparations the intermediate cinnamylidene-malonic acid was isolated and hydrogenated in cellosolve solution over palladised strontium carbonate. The product could then be decarboxylated by boiling the solution for 1 hour. Cinnamylidenemalonic acid was also decarboxylated directly by refluxing in pyridine or quinoline, but much tar was formed and the product was contaminated with an unidentified by product, m.p. 137-139° (long white needles from benzene or glacial acetic acid).

2:3-Benzosuberone -(1) XXVI (Plattner[71]).

19.6 g. phenylvaleric acid was treated with 20 ml. thionyl chloride, warmed on the water bath till evolution of HCl commenced and the reaction allowed to proceed without heat. When evolution of HCl ceased the mixture was warmed 10 minutes on the boiling water bath and the excess thionyl chloride removed in vac. The remaining pale yellow chloride was dissolved in 1 l. CS_2 (dried over and re-distilled from aluminium trichloride) and dripped into 500 ml. carbon disulphide and 28 g. aluminium trichloride at simmering point, with vigorous stirring. The addition took about 40 hours and was followed by a further 2 hours' stirring. Most of the carbon disulphide was then distilled off and the residue treated with about 750 g. ice. This was then steam distilled until the distillate was clear (2.5 l.), the distillate saturated with salt and extracted with ether. Yield, 15.9 g. b. 143°/16.5 mm. (90%). Redistilled 15.36 g. b. 78°/0.2 mm. (87.5%). Semicarbazone m. 210-213°. (Lit.: b. 138-139°/12 mm., semicarbazone m. 216° (206-207°)).

Attempted cyclisation of phenyl-valeric acid with hydrogen fluoride.

5 g. crude phenylvaleric acid was dissolved in 15 ml. hydrogen fluoride and left 10 hours. The acid was recovered unchanged.

Cyclisation of phenyl-valeryl chloride with HF.

Phenylvaleryl chloride (5 g.) was mixed with anhydrous HF (ca 15 ml.) and allowed to stand overnight. After evaporation of the HF, the residue was extracted with Na_2CO_3 and the alkali insoluble portion separated. This latter gave a brown oil (0.567 g., 14%) which gave a semicarbazone identical with that from benzosuberone (m.p. and mixed m.p.). Phenylvaleric acid was recovered on acidifying the Na_2CO_3 extract.

Condensation of benzosuberone and ethyl succinate: ketohexahydrobenzazulene. XXXII

A mixture of benzosuberone (23.1 g.) and ethyl succinate (45 g.) was added to a chilled solution of potassium (8 g.) in t-butyl alcohol (160 ml.). After refluxing under nitrogen for 45 minutes and working up as described above this gave the crude half-ester XXXI (39.2g. = 95%), which was cyclised without further purification by refluxing 3½ hours under nitrogen with acetic anhydride (400 ml.), glacial acetic acid (200 ml.) and fused zinc chloride (4 g.). This was worked up as for ketooctahydroazulene, and distillation of the neutral residue gave a white crystalline solid, m.p. 59-61° (6.57 g.) which distilled at 143-148°/0.4 mm. This was recrystallised from petroleum (40-60°) and then aq. alcohol; white needles, m.p. 61-62° (XXXII).

(Found: C, 84.91, H, 7.01%; $C_{14}H_{14}O$ requires C, 84.84, H, 7.07%).

This ketone gave a semicarbazone which crystallised from alcohol in soft spherical clusters of needles sint. 227-230°, decomp. 236°. (Found, C, 69.73, H, 6.47, N, 16.63%; $C_{15}H_{17}ON_3$ requires C, 70.60, H, 6.67, N, 16.47%).

Sublimation of the residues left after distilling the ketone gave a few mg. yellow prisms subl. 155-160°/0.4 mm. Recrystallisation from ethanol gave colourless prisms, m.p. 199-201°. (Found, C, 75.42, H, 5.65%). This compound gave a 2:4-dinitrophenylhydrazone, but only on long standing, and it was not investigated further.

The alkali soluble products were extracted with $NaHCO_3$ to remove acids, and the residue, which had a phenolic smell, was soluble in NaOH. An ethereal solution however gave no colouration with aq. $FeCl_3$.

In another cyclisation, after the alkali treatment the neutral product was extracted with $CHCl_3$. The first extract was dark brown and contained most of the product, but subsequent extracts had a deep blue-violet colour. Trial chromatograms of this solution were made, but on silica no absorption took place, while on alumina a violet band was formed which could not be eluted. Other attempts at isolating the colouring matter were unsuccessful, and on

standing for 2-3 days (in the dark) the colour vanished. This experience was not repeated in other preparations.

Attempted dehydrogenation of the ketone XXXII.

The tricyclic ketone (0.3 g.) was heated in a sealed tube with selenium (0.36 g.) for 26 hours at 300-350°. Extraction of the product gave only a yellow oil with a green fluorescence (25 mg.).

Reduction of the ketone XXXII.

(i). Aluminium isopropoxide.

The tricyclic ketone (1 g.) and distilled aluminium isopropoxide (3 g.) were dissolved in dry toluene (ca 20 ml.) and refluxed for 2¼ hours. After washing free from aluminium salts the product was distilled and three fractions collected:-

(a) pale yellow oil b. 95°/0.1 mm. (Found: C, 91.30, H, 7.69%).

(b) bright orange oil b. 120°/0.1 mm. (Found: C, 88.02, H, 7.47%).

(c) crystals subl. 140-150°/0.1 mm., recrystallised from cyclohexane, m.p. 123-124°. (Found: C, 85.17, H, 7.35%).

The first two appear to be mixtures of the hydrocarbon XXXVIII ($C_{14}H_{14}$ requires C, 92.35, H, 7.69%) and the carbinol XXXIX ($C_{14}H_{16}O$ requires C, 84.00, H, 8.00%).

(ii). PtO_2 hydrogenation.

The tricyclic ketone (2 g.) was dissolved in glacial acetic acid (15 ml.) and hydrogenated over Adams' PtO_2 catalyst (20 mg.). Absorption took place at 100 ml./hr. until 1 double bond had been saturated; it then slowed to 40 ml./hr. until 2 double bonds had been saturated and then absorption was very slow until after 16 hours, 3 molecules H_2 had been absorbed and absorption stopped.

The product on distillation gave two fractions:-

(a) mobile, colourless b. 105-110°/0.6 mm. (1.14 g.) (Found: C, 86.70, H, 9.08%)

(b) viscous, colourless b. 115-120°/0.6 mm. (0.72 g.) (Found: C, 82.42, H, 8.44%).

These are probably mixtures of the saturated hydrocarbon and carbinol corresponding to XXXVIII and XXXIX respectively.

($C_{14}H_{18}$ requires C, 90.33, H, 9.68%; $C_{14}H_{18}O$ requires C, 83.16, H, 9.78%).

(iii). Raney nickel hydrogenation.

The tricyclic ketone (1 g.) was hydrogenated in alcohol solution over Raney nickel (Pavlic and Adkins[79]). Absorption stopped after 5 hours, when 2 mols. hydrogen had been absorbed. The product was distilled and gave an apparently homogeneous, very viscous liquid b. 105°/0.2 mm.

(Found: C, 80.70, H, 7.93%).

Dehydrogenation of the reduction products.

The low boiling fraction (a) of the PtO_2 reduction product (0.84 g.) was heated under reflux with selenium (1 g.) at 330-360° for 3 days. The material became very dark brown and tarry and was extracted with $CHCl_3$, the extract being chromatographed on a short alumina column to remove colloidal selenium. After evaporation of the solvent the residue was extracted in a Soxhlet with petroleum but the extract was only light orange in colour (green fluorescence).

Dehydrogenation of the same material with palladium black at 320-330° for 4½ hours and distillation of the product gave only a colourless distillate.

Dehydrogenation of the mixture of PtO_2 reduction products with sulphur (75% of theoretical) at 220-300° led to the evolution of H_2S. On distillation some starting material was recovered, but extraction of the residue with $CHCl_3$, evaporation of the solvent, extraction of the residue with petroleum and chromatography of this solution on alumina gave a pink band on the column. This was eluted with benzene-petroleum to give a dark red solution which did not have an azulene spectrum, but had a strong absorption band at 5428 Å. No trinitrobenzene complex of this material

could be obtained.

The Raney nickel reduction product was refluxed with selenium at ca 400° for 5 hours. Evolution of H_2Se was fairly vigorous at first, but the product was viscous and tarry and gave no azulene.

This reduction product was also vapourised over 10% palladium charcoal in the vapour phase apparatus A at 430° but the distillates were colourless.

Addition of diazoacetic ester to 2-methylindane.

To 2-methylindane (68 g.) in a Claisen flask was added diazoacetic ester (10 g.) during 1 hour, the temperature being maintained at 130-140°. A very slow evolution of gas took place. The temperature was raised to 165° during 15 minutes, the evolution of gas becoming more violent, and was maintained there for 2 hours. The unchanged indane was distilled and re-treated with more diazoacetic ester, a total of 14 additions being made using 83 g. diazoacetic ester. 16.2 g. indane was recovered b. $<$ 125°/15 mm.

The addition product was now distilled and gave (1) 8.5 g. b. $<$ 140°/4 mm., (2) 34.7 g. b. 140-155°/3 mm., (3) 5.3 g. b. 165-175°/4 mm., (4) 57.4 g. residue.

Hydrolysis of the addition product.

The addition product (middle fraction, 22 g.) was refluxed 14 hours with alcoholic potash (175 ml. 96% EtOH, 19 ml. H_2O and 11.5 g. KOH). The alcohol was distilled and the residue diluted with water and extracted with ether. This gave only ca 30 mg. residue on evaporation; acidification of the alkaline layer followed by extraction gave the crude acid (18.12 g., viscous brown liquid, 95%).

Dehydrogenation of hydrolysed addition product: 2-methylazulene.

The acid (19 g.) was dehydrogenated over 10% palladium charcoal supported on asbestos, at 280-300° in the vapour phase apparatus (diagram C). The product was dissolved in petroleum and extracted with 85% H_3PO_4, which was then washed with petroleum, diluted with water and extracted with ether. The ether was then washed with Na_2CO_3 solution to remove acids. This gave 0.91 g. material, while 1.47 g. neutral material remained in the ether. 9.42 g. remained insoluble in H_3PO_4.

The neutral fraction was dissolved in petroleum and chromatographed on 25 g. alumina (activity II - I), washing with petroleum being continued until the violet colour changed to blue. Evaporation gave 2-methylazulene (1.06 g.) which crystallised on cooling.

Recrystallised from aq. alcohol, blue-violet leaflets m.p. 46.5° (corr.). (Found: C, 92.12, H, 7.39%; calc. for $C_{11}H_{10}$: C, 92.91, H, 7.09%).
Spectrum: 673 ff, 649 s, 610.5 ff, 590 m, 562 ff, 523 ss (petroleum).

The trinitrobenzene complex crystallised from alcohol in brown needles, m.p. 141-142° (corr.).
(Found: C, 57.43, H, 3.63%; calc. for $C_{17}H_{13}O_6N_3$: C, 57.46, H, 3.69%).

Dehydrogenation of unhydrolysed addition product: 2-methylazulene-6-carboxylic ester, XLII.

The addition product (middle fraction: 42.8 g.) was dehydrogenated in the vapour phase apparatus over palladium charcoal (10%) on asbestos at 300-310° during ca 3 hours. A deep blue condensate (39.1 g.) was obtained and extracted with H_3PO_4, giving a greenish brown neutral fraction (8.1 g.), some acidic material extractable with Na_2CO_3 (100 mg.) and 30 g. H_3PO_4 insoluble material.

The neutral material was extracted with petroleum and chromatographed on alumina (80 g.). A blue oil was obtained (3.2 g.) which was re-chromatographed and then distilled, b.p. 130°/0.1 mm. (2.24 g.). (Found: C, 77.99, H, 6.69%; $C_{14}H_{14}O_2$ requires: C, 78.48, H, 6.59%).
Spectrum: 752 f, 716 m, 670 m, 653 f, 628 m, 614 m, 594 ff, 572 m, 560 s, 549 f (petroleum).

The trinitrobenzene derivative formed brown needles m.p. 65-65.5°, which were more soluble in alcohol than trinitrobenzene itself. (Found: C, 56.27, H, 3.96, N, 9.88%; $C_{20}H_{17}O_8N_3$ requires: C, 56.21, H, 4.01, N, 9.83%).

A clean separation of ester from trinitrobenzene could not be obtained by chromatography on neutral or alkaline alumina, using petroleum, benzene or cyclohexane as solvents since the two components were adsorbed with approximately the same strength.

In other preparations of the ester, traces of the violet 2-methylazulene were obtained, and also a blue material. Spectrum: 722 ff, 686 m, 649 ff, 616 m, 587 ff, 561 s, 538 s, 524 ss, 506 ss (2-methylazulene-5-carboxylic ester?).

Hydrolysis of 2-methylazulene-6-carboxylic ester - 2-methylazulene-6-carboxylic acid XLV.

The ester (530 mg.) was refluxed 3 hours with alcoholic potash (1%: 30 ml.). Water was added, the alcohol distilled, and the solution extracted with ether, which removed only a trace of green material. The aqueous layer on acidification gave a dark green solid (380 mg.) which crystallised from a large volume of cyclohexane in dark blue-green crystals m.p. 164-165°. (Found: C, 76.82, H, 5.09%; $C_{12}H_{10}O_2$ requires: C, 77.40, H, 5.41%).

Spectrum: 654 ff, 631 s, 594 ff, 574 s, 550 m. (alcohol).

Attempted preparation of acid chloride and amide from 2-methylazulene-6-carboxylic acid.

The acid (150 mg.) was dissolved in dry ether (10 ml.) and thionyl chloride (0.15 ml.) in dry ether (5 ml.) added with shaking. After standing ½ hour in the cold, the solution, which was now deep red, was poured into an ethereal solution of ammonia (10 ml.) with cooling in ice. A green precipitate formed, insoluble in solvents other than alcohols. The solution was evaporated and the residue and precipitate dissolved in methanol/ether and chromatographed on alumina. A small amount of the original acid (identified by spectrum) was recovered by elution with ammonia, but the majority of the material could not be eluted from the alumina.

Attempted preparation of the amide from the ester.

The ester (55 mg.) was dissolved in ethanol (2 ml.), the solution saturated with ammonia gas and allowed to stand 5 days in the cold. A portion was then evaporated but the residue was liquid. After a further 2 days the solution was refluxed 3 hours and then evaporated, but the residue was still liquid and soluble in petroleum. Chromatography on alumina showed that the material was practically homogeneous,

only a trace remaining on the column after washing with benzene. The spectrum of the eluate was identical with that of the starting material.

2-Methylazulene-6-carboxylic amide XLIII.

The ester (155 mg.) was dissolved in 96% ethanol (ca 1 ml.), a few drops of ethylene glycol added, the solution saturated with ammonia gas and heated 23 hours at 190° in a sealed tube. The alcohol was then evaporated, the residue dissolved in $CHCl_3$ and washed with dil. Na_2CO_3 solution which removed some blue-green acid (30 mg.). Spectrum: 652 m (628?), 595 f (572?), 549 f.

The $CHCl_3$ layer was evaporated and gave a solid residue (100 mg. = 76%). This was separated into two fractions by crystallisation from ethanol:

1). violet plates m.p. 225-227° (small quantity)
(Found: C, 72.34, H, 6.03, N, 8.53%),

2). blue plates m.p. 212-214° (main fraction)
(Found: C, 77.92, H, 5.99, N, 7.61%; $C_{12}H_{11}ON$ requires: C, 77.84, H, 5.95, N, 7.57%).

Spectrum: 664 m (642?), 606 f (583?), 557 f (alcohol).

Subsequent preparations in which 99% ethanol was substituted for 96% were unsuccessful.

In an early experiment, conducted at 140° for 6½ hours, a bright green acid was obtained, m.p. 215-220°

decomp.; mixed with the dark blue-green acid (m.p. 162-164°) from the hydrolysis of the ester m.p. ca 160° decomp. Spectrum: 669 m, 607 m, 558 s.

On treatment with diazomethane this gave a blue solid ester spectrum: 676 f, 651 s, 636 s, 613 m, (577 ss), (564 ss),(542?) (petroleum).

The by product from later amide preparations appeared to be a mixture of the two acids.

Attempted Hofmann reaction on 2-methylazulene-6-carboxylic amide.

A stock solution of 0.5 N NaOCl was prepared by absorbing the chlorine from 21 ml. HCl and 1.615 g. $KMnO_4$ in 100 ml. 10% NaOH (see Adams: Organic Reactions, vol.III). The effect of this solution on guajazulene was tried by dissolving 100 mg. of the latter in 1 ml. dioxane, adding 2 ml. NaOCl solution and allowing this to stand at 30-40° for 2½ hours. The azulene was recovered unchanged.

The crude amide (175 mg.) was kept at 35° for 2 hours with 0.5 N NaOCl solution (4 ml.). The solid did not dissolve, but turned brown. No HCl soluble material was obtained and most of the amide (120 mg.) was recovered.

This recovered amide (120 mg.) was dissolved in

methanol (ca 5 ml.), NaOCl solution (2.7 ml.) added and the mixture warmed on the water bath for a few minutes. The colour rapidly changed to purple and a brown gum was deposited. After ca 10 minutes the mixture was diluted with water and the methanol distilled. The aqueous layer was extracted with ether and then $CHCl_3$, then acidified and extracted again. The latter extract gave some black solid (70 mg.) which on recrystallisation from cyclohexane gave green crystals m.p. 155-160° (41 mg.) apparently identical with 2-methylazulene-6-carboxylic acid.

The first extract (purple) gave a dark purple solid (50 mg.) which was dissolved in a little ethanol and treated with dil. H_2SO_4, but no coloured acid soluble material was obtained. The original material was recovered and chromatographed giving:

1) blue oil (10 mg.)
2) pink, semi-solid (30 mg.)
3) green-brown, gum (trace)
4) blue solid (10 mg.) - unchanged amide.

Attempted reduction of the amide with lithium aluminium hydride.

The amide was treated with excess $LiAlH_4$ in ether and a brown complex was formed, but on hydrolysing this no

acid soluble material was obtained, the starting material being recovered unchanged. When some dry benzene was added to increase solubility, and the solution warmed for a few minutes, a trace of pink material soluble in acid was obtained, but the bulk of the amide was recovered unchanged. When the reaction was performed in benzene and the complex refluxed 2 hours, the blue colour was destroyed completely and no acid soluble material was obtained, a brown gum remaining in the neutral fraction of the product.

Reduction of 2-methylazulene-6-carboxylic ester with $LiAlH_4$: 2-methyl-6-hydroxymethylazulene, XLVIII.

The ester (200 mg.) dissolved in dry ether (ca 20 ml.) was placed in a flask fitted with condenser and dropping funnel protected by drying tubes. An ethereal solution of $LiAlH_4$ (3.5 mg./ml. : 4 ml.) was dropped in with shaking. A purple complex was deposited and allowed to stand overnight. A few drops of water were then added, the excess removed with Na_2SO_4 and the solution filtered and evaporated. The residue (violet) was only sparingly soluble in petroleum and was dissolved in benzene and chromatographed giving:

1) a trace : blue : spectrum 692 ff, 670 m, 649 s, 626 ff, 611 m, 591 m, 575 f, 559 s, 542 s, 532 s (2:6-dimethyl-azulene?)

2) 80 mg. : blue-violet : spectrum 658 f, 635 s, 599 f, 578 s, 551 f, 511 ss (unchanged ester)

3) 125 mg. : violet (eluted with ether) : spectrum 654 ss, 601 m, 561 m.

Recrystallisation of fraction 3 from cyclohexane gave dark purplish black prisms of 2-methyl-6-hydroxymethylazulene m.p. 124-125°.

(Found: C, 83.44, H, 7.23, "H" (Zerewitinoff) 0.61%; $C_{12}H_{12}O$ requires: C, 83.69, H, 7.02, "H" 0.59%).

Similar reduction of the free 2-methylazulene-6-carboxylic acid gave a violet oil but the product was not crystallised.

A subsequent reduction of the ester using a large excess of $LiAlH_4$ gave no unchanged ester, but much green brown by product.

Treatment of the alcohol with benzoyl chloride and pyridine in ether gave a blue-violet oil which could not be crystallised. The reaction was fairly vigorous and the alcohol does not appear to be very stable as it resinifies readily in air.

Table of Spectra.

These spectra were measured on a visual spectrometer, the centres of the bands being taken as the average of a number of determinations. Wave lengths are in mμ and the intensities of the bands are denoted qualitatively as follows: ff = very strong, f = strong, m = medium, s = weak, ss = very weak

1	2	3	4	5	6	7	8
Ester XLII	Acid XLV	Acid (from amide prep.)	Ester (from acid 3)	Amide XLIII	Alcohol XLVIII	2-Methyl azulene	Hydrocarbon (from ester + $LiAlH_4$) XLIX
(Petr.)	(EtOH)	(EtOH)	(Ether)	(EtOH)	(Ether)	(Petr.)	(Petr.)
751 f							
716 m							692 ff
670 m		669 m.	676 f	664 m		673 ff	670 m
653 f	654 ff		651 s		654 ss	649 s	649 s
				(642 ?)			
628 m	631 s		636 s				626 ff
614 m		607 m	613 m	606 m		611 ff	611 m
					601 m		
594 ff	594 ff					590 m	591 m
				(583 ?)			
572 m	574 s		(577 ss)				575 f
560 s		558 s	(564 ss)	557 f	561 m	562 ff	559 s
549 m	550 m						
			(542 ?)				542 s
							532 s
						523 ss	

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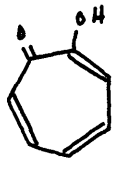
Part II - Tropolones.

Summary.

A synthesis of 3:4-benztropolone (3:4-benzcyclohepta $\Delta^{3:5:7}$-trien-1-ol-2-one XXX) is described. 2:3-Benzsuberone is oxidised with selenium dioxide to the α-diketone XXIX, which is then dehydrogenated with palladised charcoal in trichlorobenzene to benztropolone. Fusion of this with potash gives α-naphthoic acid, while the presence of the 7-membered ring is confirmed by hydrogenation to 3:4-benzsuberan-1:2-diol XXXII which is oxidised by hypobromite to the known γ-2-carboxyphenylbutyric acid XXXIII and by periodic acid to γ-2-formylphenylbutyraldehyde XXXIIIa. Benzsuberandione has also been brominated to a mixture of a monobromobenzsuberandione and a monobromobenztropolone, and the latter has been debrominated to benztropolone.

Palladium dehydrogenation of suberandione has not been similarly successful in producing tropolone, but bromination has resulted in a bromotropolone, which however has not been debrominated.

The name "tropolone" was suggested by Dewar[86] for the cyclo heptatrienolone system I, and this structure has certain unique features. Although it is the mono-enol form of the diketone III, the conjugation of the three double bonds and the keto group to form a closed system, and the possibility of resonance with the alternative form II, lead one to expect a greater stability than is usual in the mono-enol forms of α-diketones. In fact, the enolone system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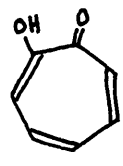
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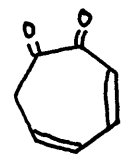
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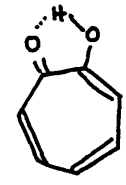

IV

may be considered as an extended form of the carboxyl or β-diketone groupings:-

O = C - OH, O = C - C = C - OH, O = C-C = C-C = C-C = C-OH
carboxyl β-diketone tropolone

from which might be expected a considerable degree of acidity, and Dewar suggested in addition that the closed system I should exhibit quasi aromatic properties, with suppression of both carbonyl and double bond reactivity.

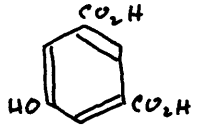
His original theory also included the existence of a hydrogen bond as in IV, which would increase the resonance energy and hence the stability, but calculation of the O - O bond distance has shown that it may be too long to permit an

ordinary hydrogen bond[87].

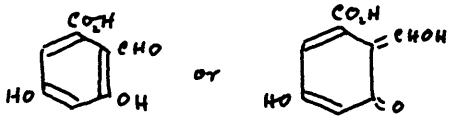
Stipitatic acid.

The occasion for this speculation was the discovery of a mould metabolite, stipitatic acid, which was very fully described and characterised, together with some of its derivatives, by Birkinshaw, Chambers and Raistrick in 1942[88]. Although this substance has the apparently simple molecular formula $C_8H_6O_5$, these authors were unable to establish a satisfactory structure for it. It titrates as a dibasic acid and a neutral solution of its sodium salt is strongly yellow. It dissolves in conc. HCl or HNO_3 to give a yellow solution from which it can be regenerated by dilution, suggesting the formation of an oxonium salt. No aldehyde or keto group could be detected with a wide variety of reagents. Two of the oxygen atoms were shown to be in a carboxyl group, and the presence of a phenolic hydroxyl and a strongly acidic-enol group was also demonstrated. The fifth oxygen atom was unaccounted for until it was found that on hydrogenation a tetrahydrostipitatic acid was formed which was ketonic and only a mono basic acid. This suggested the presence of a carbonyl group whose activity was masked in some way in the original compound. The general stability of the material suggests an aromatic

compound - bromine for example forms a mono substitution compound which is not readily hydrolysed - and a striking fact is that fusion with potash at 300° gives an excellent yield of the isomeric 5-hydroxy iso phthalic acid V.



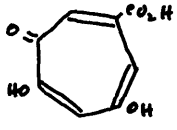
V



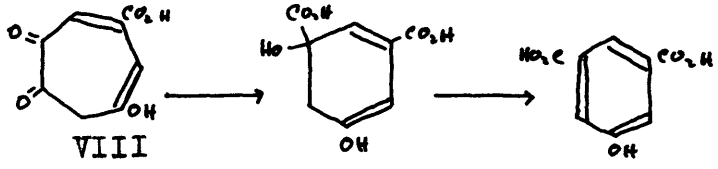
VI

The only formula which Birkinshaw, Chambers and Raistrick were able to suggest was 2-formyl-3:5-dihydroxy benzoic acid VI, but on synthesis this compound proved to be different, and in fact gave typical aldehyde reactions.

Dewar now proposed a hydroxy tropolone structure VII. The second acidic function and the masked carbonyl reactivity are explained by the - enolone grouping, and the stability of the substance by the resonance described previously. 5-Hydroxy-iso-phthalic acid is produced by benzilic acid rearrangement of the diketo form VIII



VII

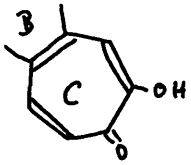


VIII

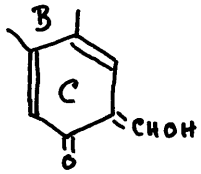
Confirmation of this structure has recently (Sept.1949) been claimed by Todd et al[106], who have obtained aconitic acid, $HO_2C.CH:C(CO_2H).CH_2.CO_2H$, by oxidation of stipitatic acid. These workers have also shown that two other fungus products - puberulic and puberulonic acids - have a tropolone structure.

Colchicine.

Shortly after these speculations, Dewar[89] put forward the suggestion that ring C of colchiceine might also have a tropolone structure, and that colchicine and iso colchicine were the two possible isomeric methyl ethers. This would explain the acidity of colchiceine, the formation of isomeric dibenzenesulphonates, the intense ferric reaction which is not given by colchicine, the intense yellow colour of its alkaline solutions, and the formation of a yellow dihydrochloride. The lack of carbonyl reactivity is also explained much more satisfactorily than by the original hydroxymethylene ketone formula of Windaus[90], as is the stability of the double bonds towards maleic anhydride and perbenzoic acid.

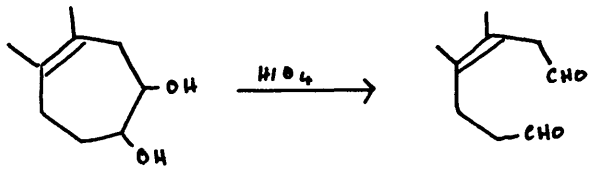


Dewar

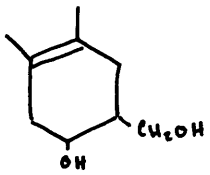


Windaus

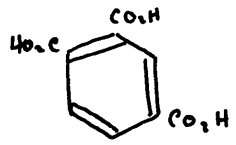
Further evidence is provided by hydrogenation[91], which produces a new hydroxyl function, the product giving a carbonyl compound with periodic acid, as would be expected from the α-glycol IX, though probably not from the β-glycol IXa. Further evidence on this point is discussed later. Alkali fusion followed by $KMnO_4$ oxidation gives trimellitic acid X[92], which could be formed from ring C by benzilic acid rearrangement.



IX

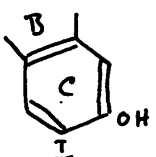


IXa

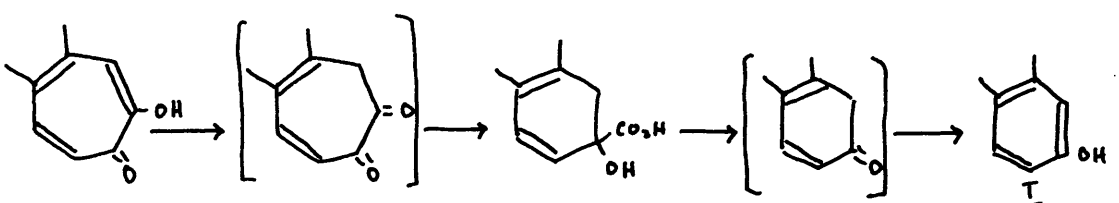


X

A more difficult reaction to explain is the conversion of colchiceine with cold hypoiodite or hypobromite into a compound in which ring C is almost certainly benzenoid, viz. XI[92,93]. Dewar accounts for this by benzilic acid rearrangement followed by oxidation and halogenation,



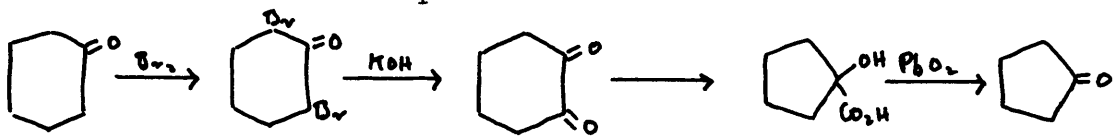
XI



I

but the reaction conditions are very much milder than those usually associated with the benzilic acid change, and evidence which has subsequently been obtained from known tropolones suggests that these are very stable to alkali. On the other hand Wallach[94] has converted substituted cyclohexanones to the cyclopentanones by successive bromination and shaking with

alkali in the cold, though the final oxidation had to be carried out with lead peroxide.

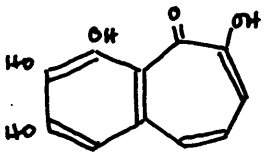


Despite this possible objection, the tropolone structure appears to be the most satisfactory yet suggested for ring C of colchiceine.

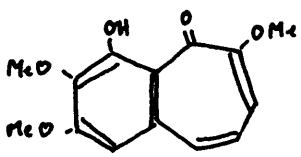
Purpurogallin.

The first natural product to which a tropolone structure was definitely assigned was purpurogallin. This compound is obtained by oxidation of pyrogallol and also from certain naturally occurring galls, and the work of Barltrop and Nicholson[95], and Haworth and co-workers[96] has shown it to have the trihydroxy benztropolone structure XII.

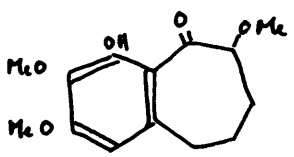
Methylation of purpurogallin gives a trimethyl derivative XIII, which can be hydrogenated to a ketonic tetrahydrotrimethyl purpurogallin XIV, and this further methylated to the tetramethyl compound XV. Oxidation with alkaline peroxide now gives the trimethoxycarboxy-phenylbutyric acid XVI which has been identified by synthesis.



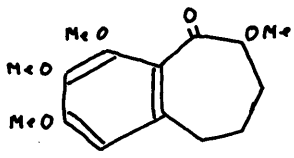
XII



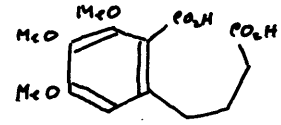
XIII



XIV

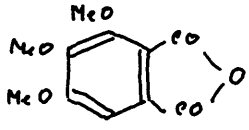


XV

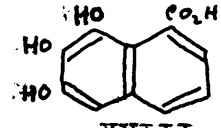


XVI

Oxidation of tetramethyl purpurogallin with $KMnO_4$ gives trimethoxyphthalic anhydride XVII, while fusion of purpurogallin with potash gives purpurogallone, which is believed to be the trihydroxy - α -naphthoic acid XVIII arising from benzilic acid rearrangement and dehydration.

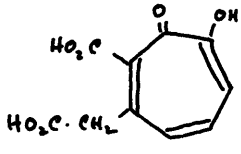


XVII

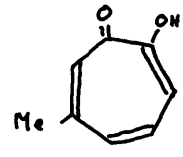


XVIII

Aerial oxidation of purpurogallin results in fission of the benzene ring, leaving a tribasic acid which can be decarboxylated by heating to a monobasic acid. These compounds are stated to have properties similar to stipitatic acid, and are believed to be the simple tropolone derivatives XIX and XX respectively.



XIX

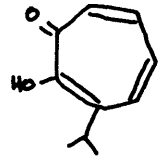


XX

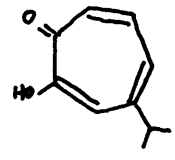
Purpurogallin itself and its methyl ethers have no ketonic properties, but their hydrogenation products are ketonic.

Thujaplicins.

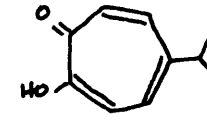
One other group of natural products has been shown to have the tropolone structure. The three possible isopropyltropolones XXI, XXII and XXIII have been isolated by Erdtman and his co-workers[97] from western red cedar (thuja plicata D.Don, Cupressaceae) and are designated respectively α-, β- and γ-thujaplicins.



XXI

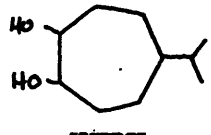


XXII

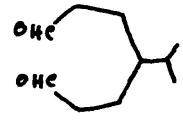


XXIII

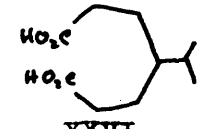
They show no carbonyl reactivity, but hydrogenation gives first a ketonic product and then a glycol XXIV which can be oxidised with periodic acid to the dialdehyde XXV, or with permanganate to the dibasic acid XXVI which can then be ring closed to the isopropylcyclohexanone XXVII, thus establishing a 7-membered ring in the original. Alkali fusion gives the corresponding isopropylbenzoic acid.



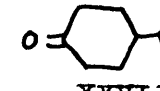
XXIV



XXV



XXVI



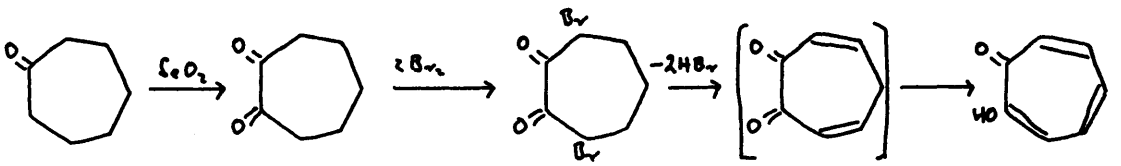
XXVII

These thujaplicins are toxic to a variety of wood-destroying moulds and account for the great durability of the wood in which they occur.

Synthesis.

The present work is concerned with attempts to synthesise the tropolone structure in order to make a direct study of its properties and compare them with those of colchiceine.

The scheme originally devised was to oxidise suberone to the α-diketone XXVIII with selenium dioxide, brominate this and then dehydrobrominate to tropolone itself:-



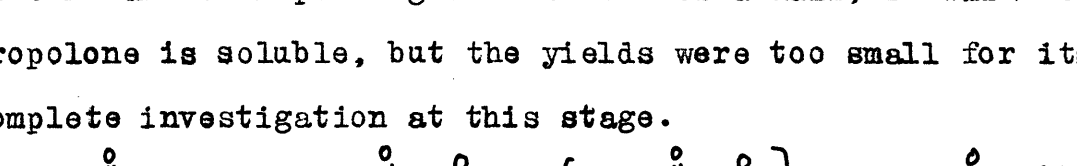
XXVIII

The diketone was obtained as a deep yellow liquid b.p. 104-110°/17 mm., but bromination of this with 2 molecules of bromine at low temperatures gave only oily products, though the use of excess bromine gave a crystalline tetrabromide m.p. 82-84°, but this gave only tarry products on attempting to debrominate it with pyridine.

The same series of reactions was now tried on benzsuberone, in the hope of obtaining more stable, crystalline compounds. Selenium dioxide oxidation gave the diketone XXIX as a deep yellow liquid b.p. 128-132°/0.4 mm., from which was obtained a mono 2:4-dinitrophenylhydrazone m.p. 230-232°, and a semicarbazone m.p. 190-192°. Neither this diketone nor suberandione formed a quinoxaline with o-phenylenediamine.

Benzsuberandione reacted readily with 1 molecule of bromine in glacial acetic acid and two crystalline monobromo compounds, m.p. 142-144° and 92-94° respectively, at first thought to be isomeric, were obtained. Numerous attempts were now made to debrominate these compounds, by heating with pyridine, quinoline or sodium acetate, or condensation with di- or tri-methylamine followed by exhaustive methylation, but without success. The lower melting compound was much the less stable, and appeared to form an amine with dimethylamine, which the higher melting compound did not. The procedure of Mattox and Kendall[98] for debrominating α-bromoketones by treatment with dinitrophenylhydrazine was also unsuccessful.

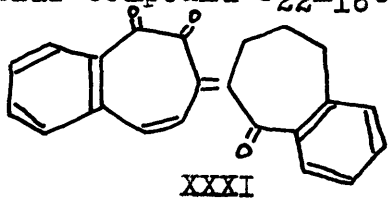
In some brominations of benzsuberandione a bromine-free byproduct was obtained in small amounts, and this subsequently proved to be the desired benztropolone XXX. Its formation in this reaction is favoured by heating the mixture and then pouring it into excess alkali, in which the tropolone is soluble, but the yields were too small for its complete investigation at this stage.



XXIX XXX

Direct dehydrogenation of benzsuberandione by refluxing with palladised charcoal in trichlorobenzene was now tried.

This led to a mixture of products, a neutral solid m.p. 270-271° which precipitated during the working up and analysed for a bi-molecular compound $C_{22}H_{16}O_3$, possibly XXXI;

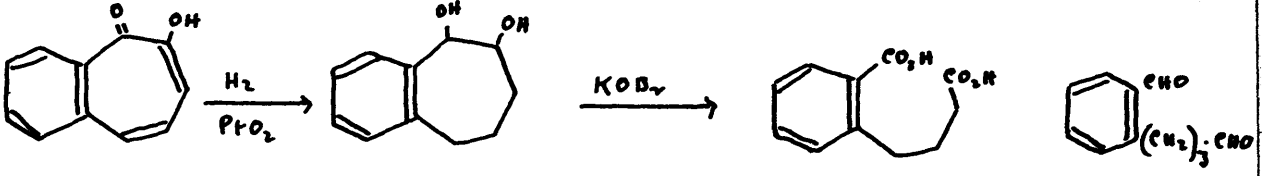


XXXI

an acid removed by washing with bicarbonate solution, m.p. 136-138°; and about 10% of benztropolone, extracted by washing with alkali. This formed pale yellow needles, m.p. 85-86° which gave a blood-red colouration with ferric chloride, a crimson precipitate with p-tolyl diazonium chloride, and which dissolved in caustic alkali, though not in carbonate, or in conc. HCl to give yellow solutions. The HCl solution became colourless on dilution with water and the material was reprecipitated. Benztropolone had no carbonyl reactivity: it could not be condensed with 2:4-dinitrophenylhydrazine or semicarbazide, and itwas recovered unchanged after heating with hydroxylamine hydrochloride in alkali (the method used by Wallach[99] to form derivatives of diosphenols). With acetic anhydride a gummy material was formed which gave no ferric chloride reaction, but could be hydrolysed to the original tropolone with caustic soda. With aqueous copper acetate solution a chloroform soluble copper salt was formed which crystallised in dark olive green needles m.p. 249-250°,

and from which the original benztropolone could be regenerated with HCl.

Fusion of benztropolone with caustic potash gave an almost quantitative yield of α-naphthoic acid. The presence of a 7-membered ring was confirmed by hydrogenation with Adams' catalyst to the diol XXXII which gave a characteristic colour with Criegee's[100] α-glycol reagent, potassium tetramethyl osmate $Os(OCH_3)_4(OK)_2$, and which was oxidised by potassium hypobromite to the known γ-2-carboxyphenyl-butyric acid XXXIII. This acid was also obtained by HNO_3 oxidation of benzsuberone[101] and by oxidation of benzsuberandione with alkaline hydrogen peroxide, by which the diol was unaffected.

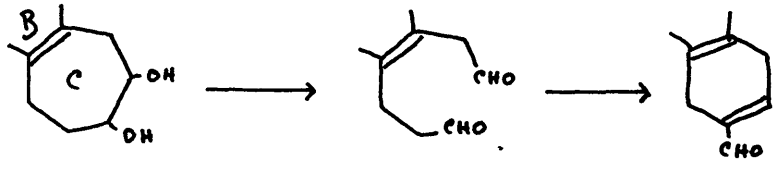


XXXII XXXIII XXXIIIa

The masked carbonyl reactivity of benztropolone was revealed by hydrogenation over palladised charcoal to a ketonic product, probably the α-hydroxy ketone, which was oxidised by alkaline hydrogen peroxide to γ-2-carboxyphenyl-butyric acid.

The diol obtained above has a very unsharp melting point (110-123°), probably due to the presence of two stereo-isomers. Similar hydrogenation of benzsuberandione with

Adams' catalyst led to a compound m.p. 120-125° which is probably the same, and this on oxidation with potassium periodate in the absence of acid gave a carbonyl compound whose semicarbazone analysed in agreement with the disemicarbazone of the dialdehyde XXXIIIa. This is interesting since under the same conditions Tarbell et al.[91] have been unable to isolate derivatives of the dialdehyde which should be the initial product of the oxidation of hexahydrocolchiceine, only a mono-aldehyde being formed, which they explain by internal ring closure:-



Failing the isolation of the intermediate dialdehyde and better characterisation of the end product than has yet been reported, however, this can scarcely be regarded as conclusive evidence for the tropolone structure of ring C.

If purified hydrogen were used for the hydrogenation of benztropolone and benzsuberandione, an uptake of nearly 7 and 5 mols. of hydrogen respectively was observed with the production of compounds m.p. 135-140° and 136-139°, mixed m.p. 125-133°. This unexpected reduction of the benzene ring increases the number of possible stereoisomers, and these compounds were not further investigated.

The behaviour of benztropolone on bromination was now investigated. 1 mol. of bromine was rapidly absorbed and the

product was found to be identical with the bromo compound m.p. 142-144° obtained from benzsuberandione. Further, this bromo compound on hydrogenation over palladium in presence of alkali gave benztropolone, so that it must be regarded as a bromotropolone. The difference in the analytical figures calculated for bromobenztropolone and bromobenzsuberandione is small and the observed values are intermediate. The observed values for the other bromo compound from benzsuberandione, m.p. 92-94° are almost identical with those calculated for a bromobenzsuberandione, and it is perhaps worth noting that this compound gives a precipitate with 2:4-dinitrophenylhydrazine while the first does not. The relative stability of the higher melting compound is also now explained.

Several variations of dehydrogenation procedure, and some other reagents were tried (see Experimental), but the yield of benztropolone could not be increased beyond 10-15%.

In an attempt to prepare benzsuberandione by an unequivocal route, isonitrosobenzsuberone (Borsche and Roth[102]) was hydrolysed in the usual way with formalin and HCl, but instead of the expected diketone a crystalline compound m.p.84-85° was obtained. This analyses in agreement with the formula $C_{13}H_{14}O_4$ (= $C_{11}H_{10}O_2$ + $2CH_2O$), but so far no structure has been assigned to it.

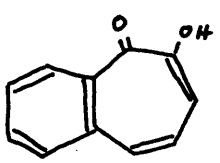
In the light of the experience gained with benztropolone, experiments were now renewed with suberandione XXVIII. By analogy with the simple tropolones from purpurogallin, it was expected that tropolone itself would be highly water-soluble and its isolation therefore more difficult than that of benztropolone. Direct dehydrogenation of suberandione with palladium charcoal gave gummy alkali-soluble products which gave a green-brown ferric chloride test but could not be purified. Heating with 2 mols. bromine in acetic acid, followed by pouring into alkali gave a monobromo compound m.p. 102-105° which analysed more closely in accordance with a bromotropolone than a bromosuberandione. This compound had no carbonyl reactivity and gave a striking deep green ferric chloride test. Although it gave no marked effervescence with bicarbonate, it imparted a yellow colour to the solution and was readily soluble in cold caustic soda or conc. HCl.

Hydrogenation of this bromo compound with palladised strontium carbonate gave a new compound m.p. ca 73-75° which had tropolone-like properties, including solubility in bicarbonate with effervescence, but still gave a test for halogen. The possibility of this latter being due to impurity however, cannot be entirely ruled out as the quantity obtained was very small and the compound difficult to purify owing to its extremely great solubility in water and alcohols, and almost complete insolubility in other solvents.

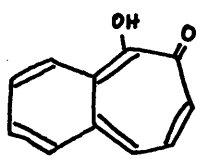
Sufficient of the material for further investigation was not obtained.

Properties.

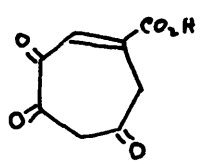
There are several obstacles in the way of attempting a direct comparison of the compounds discussed, in order to draw general conclusions about the properties of the tropolone grouping. In the first place, stipitatic acid is in a class by itself as it is really the di-enol form of a tri-ketone (XXXV) and thus has the formal structure both of an α-diketone and a β-diketone, as well as having a carboxyl group. Purpurogallin has three phenolic hydroxyls which will influence its properties considerably, and in any case, even the simple unsubstituted benztropolone cannot be considered fully representative, as the benzene ring must restrict the resonance between the two enolone forms (XXX and XXXIV), the second being much less stable, so that it may not be possible for instance to obtain derivatives of this second structure.



XXX



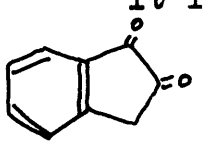
XXXIV



XXXV

However there are some general conclusions which can be drawn. The tropolones show no carbonyl reactivity.

They are remarkably stable to acids and alkalis, much higher temperatures being required to produce the benzilic acid change than is the case with α-diketones; and bromine appears to form substitution rather than addition compounds. All those tested give green chloroform soluble copper complexes, a behaviour characteristic of β-diketones, but not, apparently, of α-diketones. They all give striking ferric tests, which in the case of the simple monocyclic tropolones, are bright green, while benztropolone and the various purpurogallin derivatives are red or red-brown. In alkaline solution they give an intense yellow-green colour, but the degree of acidity varies even between such closely related compounds as the thujaplicins and the methyl tropolone from purpurogallin. Thus the latter will liberate CO_2 from carbonates, while the thujaplicins will not; also α-thujaplicin is apparently less acidic than β - or γ-, as it is precipitated first from alkaline solution. Benztropolone also is insoluble in carbonate.

It is interesting to note that diketohydrindane  , which is the next lower homologue of benztropolone, behaves as a normal α-diketone, giving the usual carbonyl derivatives, including a quinoxaline with o phenylene diamine[103]. This may possibly be due to the greater distance between the oxygen atoms.

The properties of the tropolones show a strong resemblance to those of colchiceine which gives an olive green ferric test, liberates CO_2 from carbonates, forms a chloroform soluble copper salt and on reduction gives a ketonic tetrahydro compound; but these are only useful pointers and the problem of ring C of colchicine must await further degradation experiments.

Experimental.

3:4-Benzsuberan-1:2-dione XXIX.

A solution of selenium dioxide (3.5 g.) in alcohol (35 ml.) was added in portions to benzsuberone (5 g.) over 1½ hours at the boiling point, and refluxing was continued for a total of 4 hours. The precipitated selenium was then filtered off, the alcohol evaporated and the residue distilled into two fractions:-

(1) B.p. 80-110°/0.4 mm., mobile, pale yellow (0.19 g.)

(2) b.p.128-132°/0.4 mm., more viscous, deep yellow (4.42 g. = 81%).

The latter gave a mono-2:4-dinitrophenylhydrazone, m.p. 230-232°, (Found: C, 57.53, H, 3.95, N, 15.78%; $C_{17}H_{14}O_5N_4$ requires C, 57.63, H, 3.96, N, 15.82%), and a semicarbazone m.p. 190-192°. Conversion of the entire distillate from other oxidations to the semicarbazone, and fractional crystallisation of this from ethyl acetate showed that, apart from a small amount of unchanged benzsuberone, the product is homogeneous. Sublimation in vac. of the residues from the distillation gave yellow crystals m.p. 123-125° after recrystallisation from cyclohexane.

Benzsuberandione couples with p tolyl diazonium chloride in alkaline solution to give a red precipitate. It could not be condensed with o phenylenediamine in alcohol/pyridine.

Oxidation of benzsuberandione with alkaline hydrogen peroxide.

Benzsuberandione (113 mg.) was suspended in water (1 ml.) and 30% H_2O_2 added (1 ml.). On the addition of dilute NaOH solution (2 ml.) a vigorous reaction set in. After standing 2 days in the cold this was extracted with ether to remove undissolved material, and then acidified. This gave a solid acid (92 mg. = 70%) which was recrystallised from water and then benzene/petroleum giving fine white needles m.p. 138-139°. (Found: C, 64.07, H, 6.28%; $C_{11}H_{12}O_4$ requires C, 63.45, H, 5.81%).

This was identical with the acid obtained by oxidising benzsuberone with 2½% HNO_3, mixed m.p. 134-136° (lit. γ-2 carboxyphenylbutyric acid, m.p. 138-139°).

Dehydrogenation of benzsuberandione - 3:4-benztropolone XXX.

Benzsuberandione (3.2 g.) was refluxed 8 hours under nitrogen with 10% palladium charcoal (2 g.) in 1:2:4-trichlorobenzene (20 ml., b.p. 213°). The catalyst was now filtered off, and the solution washed with sodium bicarbonate solution which removed 115 mg. of acid m.p. 136-138° after crystallisation from petroleum (80-100°): a higher melting compound m.p. 182-185° was also obtained by trituration of the crude acid with ether. The trichlorobenzene solution was next washed with 10% KOH solution, and an insoluble

crystalline precipitate filtered off. This was recrystallised from glacial acetic acid and formed pale yellow prisms m.p. 270-271° which gave a bright orange colour with conc. H_2SO_4, but no ferric chloride colouration. (Found: C, 80.49, H, 5.07%; $C_{22}H_{16}O_3$ requires C, 80.47, H, 4.91%). In other experiments this substance occasionally crystallised from the reaction mixture.

The bright yellow KOH solution was now acidified and extracted with ether, the extract evaporated and the gummy residue extracted with boiling cyclohexane. Evaporation of the latter extracts to crystallising point gave crude benztropolone (500 mg.) which was recrystallised from aq. methanol or cyclohexane forming pale yellow needles m.p. 85-86°. (Found: C, 76.33, 77.01; H, 4.71, 4.56%, M (Rast) 186; $C_{11}H_8O_2$ requires C, 76.73, H, 4.68%, M, 172). With Pd in glacial acetic acid 3.220 mg. absorbed 1.420 ml H_2/766 mm./22° = 3.13 d.b. With PtO_2 3.320 mg. absorbed 3.400 ml. H_2/766 mm./22° = 7.3 d.b.

The use of mesitylene as solvent instead of trichlorobenzene led to a gummy product, more difficult to purify.

Benztropolone gives a blood-red colouration with $FeCl_3$ in methanol, couples with p-tolyl diazonium chloride to give a crimson precipitate, and dissolves in conc. HCl to a bright yellow solution, which is decolourised on dilution

with regeneration of the original substance. It was recovered largely unchanged after heating on the water bath for 1½ hours with excess hydroxylamine hydrochloride in KOH, and did not react with 2:4-dinitrophenylhydrazine in MeOH/H_2SO_4 or aq. HCl, or with semicarbazide hydrochloride in aq. alcohol/pyridine.

Acetylation of benztropolone.

Benztropolone (50 mg.) was dissolved in acetic anhydride (1 ml.) and a trace of pyridine added. The solution was allowed to stand 2 days in the cold and then refluxed 2½ hours. The acetic anhydride was decomposed with water and the product extracted with ether. After evaporation of the ether a gum remained which could not be crystallised. This gave no ferric chloride colouration. On shaking with cold dilute NaOH it dissolved fairly rapidly to a yellow solution which was extracted with ether and then acidified, when benztropolone m.p. 83-85° was precipitated and gave the characteristic blood-red ferric chloride test.

Copper benztropolone.

A chloroform solution of benztropolone was shaken with aq. copper acetate solution. The organic layer turned yellow-green and a solid was deposited and filtered off. Recrystallisation from chloroform gave olive green needles m.p. 249-250° decomp.

This compound (19 mg.) was suspended in ether and shaken with dil. HCl till no solid remained. Evaporation of the ether then gave benztropolone (13 mg.) m.p. 82-84°.

Fusion of benztropolone with potash:- α-naphthoic acid.

Benztropolone (26 mg.) was mixed with 80% aq. KOH (1 ml.). It did not dissolve but an orange salt was evidently formed, and its appearance did not alter on heating until 180°. After a few minutes at this temperature, the salt dissolved to an orange solution which gradually became colourless, with a small amount of brown tar remaining undissolved. After about ½ hour at 180-185° no further change was observed and heating was stopped. The melt was now cooled, dissolved in water and extracted with ether (which remained colourless) and then acidified. This gave a voluminous precipitate of α-naphthoic acid (about 20 mg.) which was recrystallised from aq. alcohol (charcoal) m.p. 156-160°, mixed with authentic α-naphthoic acid (m.p. 160-162°) m.p. 159-161°.

As a control experiment, benzuberandione (210 mg.) was heated with KOH (300 mg.) in water (0.6 ml.) on the water bath for 40 minutes. Only tarry products were obtained from which no crystalline material could be isolated.

Refluxing benztropolone in 2% methanolic KOH for 4½ hours was without effect, the starting material being recovered unchanged.

Hydrogenation of benztropolone with PtO_2: 3:4-benzsuberan-1:2-diol XXXII.

Benztropolone (50 mg.) was hydrogenated at room temperature and pressure over Adams' PtO_2 catalyst (5 mg.) in ethanol (20 ml.). 3 mols. H_2 were absorbed. The solution was filtered from platinum and the alcohol evaporated, giving an orange solid sparingly soluble in ether. Trituration with cyclohexane gave a yellowish solid (40 mg.) m.p. 112-122°. This was crystallised from petroleum and then water giving white prisms, m.p. 110-123°. Repeated crystallisation did not improve this melting point though long needles were later obtained from the mother liquors m.p. 133-138°. (Found: C, 74.32, H, 7.86%; $C_{11}H_{14}O_2$ requires C, 74.13, H, 7.92%). The compound gave a pale yellow green colour with potassium tetramethyl osmate solution.

Oxidation of benzsuberandiol with hypobromite.

KOBr solution was prepared by adding bromine (0.6 ml.) to 25% aq. KOH (10 ml.). The diol (4 mg.) was allowed to stand 2 hours with this solution (0.2 ml.). As the material

did not dissolve, the mixture was warmed until a solution was obtained and a further 0.2 ml. KOBr solution added. After standing a few days the yellow solution was extracted with ether and the aq. layer neutralised with H_2SO_3 and H_2SO_4. This gave γ-2-carboxyphenylbutyric acid m.p. 136-137°, mixed with acid from oxidation of benzsuberandione m.p. 136-138°

Alkaline hydrogen peroxide was found to be without action on the diol.

Oxidation of benzsuberandiol with periodic acid.

The diol (7 mg.) was dissolved in water (1 ml.) and a solution of KIO_4 (10mg. = 1.1 equivalents) in water (1 ml.) containing a few drops of dilute H_2SO_4 added. On standing in the cold for 1 hour a faint cloudiness had appeared which was removed by shaking with ether. $SrCO_3$ was now added to precipitate the H_2SO_4 and HIO_4. The suspension was extracted several times with ether, the solid filtered and boiled with methanol and these organic extracts were then evaporated almost to dryness and 2:4-dinitrophenylhydrazine (Brady's reagent) added. A bright orange dinitrophenylhydrazone was precipitated which did not crystallise well, but was deposited from aq. acetic acid as a flocculent precipitate m.p. 233°. It gave a deep red colour with alcoholic NaOH.

In another experiment the diol (14 mg. m.p. 120-125°, from benzsuberandione) was treated with an aqueous solution of potassium periodate (20 mg. = 1.1 mol.) in the absence of acid. After standing for 2 hours in the cold, a solution of strontium chloride was added, but as no precipitate resulted the reaction was poured into a solution containing excess semicarbazide hydrochloride and pyridine in water. A semicarbazone was precipitated and recrystallised from a large volume of alcohol m.p. 200° decomp. (Found: C, 53.02, 53.25 H, 6.14, 6.24 N, 27.68%; $C_{13}H_{18}O_2N_6$, disemicarbazone of $C_6H_4(CHO).(CH_2)_3.CHO$, requires C, 53.78, H, 6.25, N, 28.95%).

Hydrogenation of benzsuberandione.

Benzsuberandione (200 mg.) in ethanol was hydrogenated over PtO_2 (2 mg.). Cylinder hydrogen was used without purification (as in previous hydrogenations). 1 mol. hydrogen was rapidly absorbed and absorption then slowed, but was speeded by the addition of a trace of KOH until 2 mols. H_2 had been taken up. The bulk of the KOH was precipitated as K_2CO_3 with CO_2 and the solution filtered and evaporated, and the residue extracted with ether. Evaporation of the solvent gave a gum which readily solidified and could be crystallised from hot water m.p. 120-125° (softening 110°). Mixed m.p.

with diol from benztropolone (crystals from the mother liquors m.p. 133-138°) m.p. 125-132°.

In subsequent experiments, hydrogen from a generator, purified with $HgCl_2$ and $KMnO_4$, was used. Absorption was very rapid and was stopped after the uptake of 2.5 mols. On working up a solid m.p. 152-158° was obtained. If the hydrogenation was allowed to proceed to a finish however (5 mols. H_2) a solid m.p. 136-139° was obtained.

Similar hydrogenation of benztropolone with purified hydrogen led to the uptake of nearly 7 mols. H_2, and the product was a solid m.p. 135-140°, mixed with the above material m.p. 136-139° from benzsuberandione, m.p. 125-133°.

Hydrogenation of benztropolone with Pd and oxidation of the product.

Benztropolone (20 mg.) was hydrogenated in ethanol over 10% palladium charcoal (10 mg.). 2 mols. hydrogen were rapidly taken up and the product, after filtration and evaporation of the solvent, was a gum which gave an immediate precipitate with 2:4-dinitrophenylhydrazine in aq. HCl. This gum was now allowed to stand overnight with $NaOH/H_2O_2$, and after extraction of undissolved material with ether, the alkaline solution was acidified and extracted, giving γ-2-carboxyphenylbutyric acid m.p. 135-137°, mixed with previously obtained material m.p. 134-137°.

Bromination of benzsuberandione.

Benzsuberandione (2.5 g.) dissolved in glacial acetic acid (20 ml.) was treated with bromine (2.5 g. = 1 mol.) in glacial acetic acid (10 ml.). Reaction was rapid at first and was completed by warming gently on the water bath for a few minutes till the colour became pale yellow. Water was then added and a brown crystalline solid separated. This was crystallised repeatedly from cyclohexane, giving pale yellow needles m.p. 142-144°. (Found: C, 52.54, H, 2.94, Br, 31.85%; $C_{11}H_9O_2Br$ requires C, 52.16, H, 3.56, Br, 31.60%; $C_{11}H_7O_2Br$ requires C, 53.04, H, 2.83, Br, 32.08%).

Further dilution of the mother liquors gave first some oil, and then colourless flakes (0.34 g.) which were recrystallised from cyclohexane m.p. 92-94°. (Found: C, 52.17, H, 3.56, Br, 31.53%; $C_{11}H_9O_2Br$ requires C, 52.16, H, 3.56, Br, 31.60%). A mixture of these two compounds had m.p. 86-115° decomp.

In other bromination experiments a byproduct was obtained which subsequently proved to be benztropolone. Its formation was favoured by heating the reaction mixture for some time, the presence of sodium acetate and/or pouring the reaction mixture into alkali, in which case an alkali salt of the higher melting bromo-compound was usually precipitated and the tropolone was recovered from the alkaline solution.

The lower melting bromo compound was not usually formed in this case.

The higher melting bromo compound gives a brown-red colour with ferric chloride, similar to that of benztropolone, while the lower melting compound gives a yellowish brown colour. The latter gives a yellow precipitate on warming with 2:4-dinitrophenylhydrazine in aq. HCl, whith the former does not.

Attempted debrominations of bromobenzsuberandione m.p. 92-94°.

Heating the bromo compound with pyridine or quinoline on the water bath or at the boiling point for periods of 1-2 hours gave only tarry products, sometimes with a phenolic smell, from which no crystalline material could be extracted.

The bromo compound (200 mg.) was heated with a 20% solution of dimethylamine in benzene (10 ml.) in a sealed tube, the temperature being raised to 85° and then immediately allowed to cool. On evaporation of the red-brown solution, white crystals mixed with gum were obtained. These were extracted with water and dilute H_2SO_4, the solution washed with chloroform, neutralised with solid $NaHCO_3$ and extracted with chloroform. Evaporation of the solvent left a dark residue which was treated with methyl iodide in $CHCl_3$/benzene solution. After standing for 1 hour the solvents and excess MeI were evaporated and the dry residue shaken with freshly

precipitated solver oxide in aq. ethanol. The solution was then filtered and evaporated and the dark residue distilled giving a small amount of brown gum b.p. 100°/0.2 mm. which could not be crystallised.

Attempted debrominations of the higher melting bromo compound (m.p. 142-144°).

The higher melting bromo compound was refluxed with pyridine for periods up to 10 hours, and heated 6 hours at 140° with quinoline. Part of the material was usually recovered unchanged from the treatments and the remainder converted to tars from which no identifiable product could be obtained.

Numerous attempts were made to condense the compound with dimethylamine by heating with aqueous or benzene solutions of the amine, but at water bath temperature the starting material was recovered unchanged, while at higher temperatures (up to 145°), some of the material decomposed and the products could not be identified.

Condensation with trimethylamine in chlorobenzene at 100° (9 hours) was also attempted, but the starting material was recovered.

The bromo compound (100 mg.) was dissolved in glacial acetic acid (5 ml.) containing sodium acetate (170 mg.), the air replaced by nitrogen and 2:4-dinitrophenylhydrazine

(100 mg.) in glacial acetic acid (5 ml.) added (cf. Mattox and Kendall[98]). The solution was then allowed to stand 1½ hours with nitrogen passing through. On dilution with water the bromo compound was precipitated unchanged.

The compound was also recovered unchanged after heating with sodium acetate in acetic acid.

Hydrogenation of bromo compound m.p. 142-144°.

The bromo compound (100 mg.) was dissolved in methanol containing 1 mol. KOH, and hydrogenated over 10% palladium charcoal. After the uptake of 1 mol. H_2 the absorption slowed down. The catalyst was then filtered off, a few drops acetic acid added and the solvent evaporated. The residue was crystallised from aq. acetic acid and gave first some crystals of impure starting material m.p. 125-130°. Further dilution of the mother liquors then gave benztropolone m.p. 81-82°, mixed with authentic material m.p. 82-85°.

Bromination of benztropolone.

Benztropolone (100 mg.) in glacial acetic acid (1 ml.) was treated with bromine in acetic acid (30% solution, 0.31 ml. = 1 mol.). The bromine was rapidly decolourised with evolution of HBr, and the solution was warmed gently and allowed to stand for a few minutes. Water was then added and the crystalline precipitate filtered and re-crystallised

twice from cyclohexane m.p. 143-145°, mixed with the high melting compound from the bromination of benzsuberandione (m.p. 142-144°), m.p. 140-145°. Further dilution of the mother liquors gave a second crop m.p. 94-100° (crude).

Treatment of the bromo compound m.p. 142-144° with KOH.

The bromo compound (50 mg.) was dissolved in 10% KOH (10 ml.) and the solution heated on the water bath 1¼ hours. It was then filtered to remove some gelatinous precipitate, cooled and acidified giving crystals of the starting material (18 mg.) m.p. 143-145°.

Other attempts to dehydrogenate benzsuberandione.

The diketone was refluxed with chloranil in xylene for 3 hours but although some tetrachlorohydroquinone was isolated the other products were oily and could not be identified.

Treatment with N-bromo succinimide and benzoyl peroxide in carbon tetrachloride, followed by the addition of potassium acetate and acetic acid and refluxing[104], was also tried but no benztropolone could be isolated.

Heating with potassium ferricyanide in Na_2CO_3 on the water bath for 6 hours gave only gummy products.

Preparation of isonitrosobenzsuberone (method of Borsche and Roth[102]).

Benzsuberone (10 g.) was added to sodium (1.45 g., atomised under xylene) under dry ether (40 ml.), the mixture cooled in ice and freshly distilled isoamyl nitrite (7.3 g.) added in portions. After a few seconds delay a violent reaction set in and the liquid turned dark red. After this had subsided, the reaction mixture was kept in the refrigerator for 3 days, by which time all the sodium had dissolved. Ice water was now added, the aqueous layer separated, acidified with acetic acid and extracted with ether which was washed with Na_2CO_3, dried and evaporated, giving a thick oil which was cooled in a freezing mixture and triturated with CCl_4. The resulting solid was crystallised from carbon tetrachloride, pale cream needles m.p. 134-135° (lit. 133-134°).

Treatment of this monoxime with excess hydroxylamine hydrochloride in alkali gave a dioxime m.p. 188-189°/aq. ethanol which gave a yellow flocculent precipitate with nickel salts.

Attempted hydrolysis of isonitrosobenzsuberone (cf. Perkin, Roberts and Robinson[103]).

Isonitrosobenzsuberone (160 mg.) was dissolved in formalin (8 ml.) in the cold and conc. HCl (5 ml.) added

slowly with shaking. As there was no apparent reaction the solution was gently warmed (40°) and a further 3-4 ml. conc. HCl added. An oil then separated which crystallised on cooling, giving long white needles (85 mg.) recrystallised from petroleum m.p. 84-85°. (Found: C, 66.78, H, 5.98%, N nil; $C_{13}H_{14}O_4$ requires C, 66.66, H, 6.02%).

This compound gave no ferric chloride colouration and was insoluble in dilute NaOH or KOH. Fusion with KOH at 180-250° for 1 hour gave first a blue colour and then a pink colour, but on cooling and adding water the starting material was almost completely recovered unchanged.

It gave no precipitate with mercuric chloride in aqueous alcohol (test for oxazoles and isoxazoles).

Warming with 2:4-dinitrophenylhydrazine in aq. HCl gave a yellow precipitate.

Oxidation of suberone with selenium dioxide: suberan-1:2-dione, XXVIII.

A solution of selenium dioxide (20 g.) in ethanol (200 ml.) was added in portions to suberone (20 g.) over 2 hours, at the boiling point, and refluxing continued for another $2\frac{1}{2}$ hours. After filtering from selenium and evaporating the solvent, the residue was distilled in vac. giving first a pale yellow fraction b.p. $< 104°/17$ mm.

(2.5 g.) and then a deeper yellow liquid b.p. 104-110°/17 mm. (80%) (lit. 107-109°/17 mm.[105]). The latter fraction gives an oxime m.p. 173-175° after crystallisation from water (lit. dioxime m.p. 181-182°), and an extremely insoluble (di- ?) semicarbazone m.p. 222-224° decomp. It could not be condensed with o-phenylene diamine in alcohol, acetic acid or alcohol/pyridine. It was largely soluble in cold 5% KOH, but resinification took place and only a small amount of diketone could be recovered from the alkaline solution. It gives a brown colour with ferric chloride.

Attempts at dehydrogenating suberandione with palladised charcoal in trichlorobenzene gave only phenolic smelling tars, partly soluble in alkali, from which however no crystalline products were obtained.

Bromination of suberandione : tetrabromosuberandione.

Suberandione (5 g.) was dissolved in glacial acetic acid (20 ml.), cooled to 0° and bromine (25 g.) added. Vigorous reaction took place with evolution of HBr. After warming gently and allowing to stand for 1 hour the solution was flooded with water and the precipitated oil recrystallised from aq. acetic acid and then benzene/petroleum, m.p. 82-84° (3.5 g.). (Found: C, 18.46, H, 1.75, Br, 72.19%; $C_7H_6O_2Br_4$ requires C, 19.01, H, 1.36, Br, 72.40%).

This compound gives no colouration with ferric

chloride.

Attempts at debrominating this compound by heating on the water bath, or refluxing, with pyridine gave only tarry products with a phenolic smell.

Similar treatment of suberandione with 2 mols. bromine gave oils from which no crystalline product could be isolated.

Bromination and oxidation of suberandione : bromotropolone.

Suberandione (2 g.) in glacial acetic acid (10 ml.) was treated with bromine (30% solution in acetic acid, 19 ml. = 2.1 mol.). After decolourisation (in the cold), the solution was heated on the boiling water bath for ½ hour and then allowed to cool slowly during 2 hours, after which it was very dark brown in colour. It was now poured into KOH solution (80 g. in 250 ml.), the solution extracted with ether, acidified with HCl, saturated with salt and extracted with ether and ethyl acetate. The extracts were washed with saturated brine, dried and evaporated giving a brown residue which gradually crystallised. This was distilled at 90°/ 0.1 mm. giving a pale yellow liquid which solidified in the receiver and was re-crystallised from cyclohexane to give cream coloured prisms m.p. 102-105° (660 mg.).
(Found: C, 42.30, H, 2.61, Br, 39.67%; $C_7H_5O_2Br$ requires C, 41.82, H, 2.51, Br, 39.76%; $C_7H_9O_2Br$ would require

C, 41.00, H, 4.42, Br, 38.97%).

This compound is soluble in hot water but not readily in cold. It gives a yellow colour to cold $NaHCO_3$ solution, dissolves in cold NaOH to a yellow solution, and in cold conc. HCl - but with no colour. A methanol solution gives a striking green colour with aq. ferric chloride. A KOH solution with diazotised α-naphthylamine gives a red-brown colour, and a precipitate on standing. A chloroform solution (colourless) turns green on shaking with aq. copper acetate solution. No precipitate was formed on heating with 2:4-dinitrophenylhydrazine in aq. HCl or $MeOH/H_2SO_4$.

Hydrogenation of bromotropolone.

The bromo compound (150 mg.) was hydrogenated over 2% palladised strontium carbonate (300 mg.), in methanol solution. Absorption slowed after the uptake of 18 ml. (= 1 mol.) and stopped completely at 26.5 ml. (= 1.5 mol.). The solution was now filtered and some glacial acetic acid added to liberate the organic material from any strontium salt which might be formed, the solvent evaporated and the residue distilled at 150-160°/2 mm. A crystalline distillate (55 mg.) was obtained, the remainder of the material in the flask giving a strontium flame test. This distillate was re-crystallised from a very small quantity of isopropyl

alcohol, and then sublimed at 80°/0.4 mm. White needles m.p. 73-75° (softening 59°). The compound still gave the Beilstein test for halogens. (Found: C, 46.80, 47.66, H, 4.89, 5.00%).

This compound was hygroscopic, very soluble in alcohols, less so in chloroform and ether, and on heating with ethyl acetate gave a highly crystalline material which was infusible at the boiling point - possibly an addition compound. It gave a green ferric chloride test, dissolved in cold bicarbonate solution with vigorous effervescence to give a pale yellow solution, and gave no precipitate with 2:4-dinitrophenylhydrazine in aq. HCl. The copper wire (Beilstein) test and sodium fusion indicated the presence of halogen.

Comparison of the above properties with those of catechol (which also gives a green ferric test) showed the latter to be quite distinct.

A similar material was also obtained by bromination of suberandione in presence of potassium acetate.

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